UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

+ + +

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

+ + +

GENERAL AND PLASTIC SURGERY DEVICES PANEL

+ + +

August 31, 2011
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, MD 20877

PANEL MEMBERS:

JOSEPH LoCICERO III, M.D.	Chairperson
A. MARILYN LEITCH, M.D.	Voting Member
SUSAN GALANDIUK, M.D.	Voting Member
DELORA L. MOUNT, M.D.	Voting Member
MARY H. McGRATH, M.D., M.P.H.	Voting Member
NANCY N. DUBLER, LL.B.	Temporary Non-Voting Member
JASON T. CONNOR, Ph.D.	Temporary Non-Voting Member
MARGARET A. HONEIN, Ph.D.	Temporary Non-Voting Member
SEAN HENNESSY, Pharm.D, Ph.D.	Temporary Non-Voting Member
LEONARD M. GLASSMAN, M.D.	Temporary Non-Voting Member
LEIGH F. CALLAHAN, M.D.	Temporary Non-Voting Member
BARBARA I. CROUCH, Pharm.D.	Temporary Non-Voting Member
ELBERT B. WHORTON, JR., Ph.D.	Temporary Non-Voting Member
ELIZABETH C. JONES, M.D., M.P.H.	Temporary Non-Voting Member
MARLENA VEGA, M.S.W., Ph.D.	Patient Representative
MICHAEL G. HALPIN	Industry Representative
KRISTINE R. MATTIVI, M.S.	Consumer Representative
JAMES P. SWINK	Designated Federal Officer

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947

FDA REPRESENTATIVES:

MARK MELKERSON, M.S.
Director, Division of Surgical, Orthopedic, and Restorative Devices
Office of Device Evaluation

DANICA MARINAC-DABIC, M.D., Ph.D.
Director, Division of Epidemiology
Office of Surveillance and Biometrics

ERICA JEFFERSON
Press Contact

FDA PRESENTERS:

CARA J. KRULEWITCH, C.N.M., Ph.D.
Branch Chief, Division of Epidemiology
Office of Surveillance and Biometrics

OZLEM TOPALOGLU, Ph.D., M.P.H.
Division of Epidemiology
Office of Surveillance and Biometrics

SPONSOR PRESENTERS (ALLERGAN):

RUI AVELAR, M.D.
Chief Medical Officer
Allergan, Inc.

SPONSOR ADVISORS (ALLERGAN):

TODD GROSS, Ph.D.
Senior Director of Biostatistics, Allergan Medical

ARACELI SLICTON
Allergan

SPONSOR PRESENTERS (MENTOR):

JOHN CANADY, M.D.
Medical Director, Mentor Worldwide, LLC

ROGER WIXTROM, Ph.D., DABT-LSCI

SPONSOR ADVISORS (MENTOR):

NICOLA SELLEY
MICHELE BONHOMME

OPEN PUBLIC HEARING SPEAKERS:

DANA CASCIOTTI, Ph.D.
KATE RYAN
JUDITH FAUCETTE for BEATRICE RING
SUSAN A. POPE HELMAN
SHARON SCHWENGLER
MARY ROSSER FURR
JENNY KELLY
DENNIS C. HAMMOND, M.D.
AUDREY SHEPPARD
ANN PUGH
GARRY BRODY, M.D.
CAROLINE A. GLICKSMAN, M.D.
LEROY YOUNG, M.D.
PHIL HAECK, M.D.
ROBERT X. MURPHY, JR., M.D.
STEVEN BONAWITZ, M.D.
ANDREA PUSCIC, M.D.
DENNIS DEAPEN, M.D.
SALLY GREENBERG
GREGORY HOWARD

INDEX

	PAGE
CALL TO ORDER - Joseph LoCicero III, M.D.	333
PANEL INTRODUCTIONS	334
CONFLICT OF INTEREST AND TEMPORARY VOTING MEMBER STATEMENTS - James P. Swink	337
GENERAL ANNOUNCEMENTS - James P. Swink	340
RECAP OF DAY 1 ISSUES - FDA Cara J. Krulewitch, CNM, Ph.D., FACNM	341
Q&A	343
OPEN PUBLIC HEARING	
Dana Casciotti, Ph.D.	357
Kate Ryan	360
Susan A. Pope Helman	364
Sharon Schwengler	367
Q&A	370
Mary Rosser Furr	372
Jenny Kelly	375
Dennis C. Hammond, M.D.	378
Audrey Sheppard	382
Ann Pugh	383
Garry Brody, M.D.	385
Q&A	387
Caroline A. Glicksman, M.D.	390
Leroy Young, M.D.	394
Phil Haeck, M.D.	396
Robert X. Murphy, Jr., M.D.	399

INDEX (cont.)

	PAGE
OPEN PUBLIC HEARING (cont.)	
Steven Bonawitz, M.D.	403
Andrea Puscic, M.D.	406
Q&A	410
Dennis Deapen, M.D.	418
Sally Greenberg	421
Gregory Howard	423
Q&A	426
SPONSORS' RESPONSE TO PANEL QUESTIONS	435
PANEL DELIBERATIONS & FDA QUESTIONS (cont.)	
Question 2	447
FDA RESPONSE TO PANEL QUESTIONS	471
PANEL DELIBERATIONS & FDA QUESTIONS (cont.)	
Question 3	480
Question 4	487
Question 4(b)(4) and 5	519
Question 6	526
Question 7	544
Question 8	556
FDA SUMMARY	565
SUMMARY COMMENTS SOLICITED FROM PANEL	566
ADJOURNMENT	566

M E E T I N G

(8:00 a.m.)

DR. LoCICERO: Call the General and Plastic Surgery Devices Panel to order.

I am Joseph LoCicero. I am Chair of the Panel. I am a general and thoracic surgeon and Professor Emeritus of Surgery at SUNNY Downstage.

I'm going to ask everyone to introduce themselves shortly, but I would like to note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel participating in the meeting today has received training in FDA device law and regulations.

For today's agenda, the Committee will discuss and make recommendations on postmarketing issues related to silicone gel-filled breast implants, or SGBIs. This meeting is regarding an update on the status of the current postapproval studies for SGBIs and a discussion of different innovative methodological approaches to the conduct of postmarket studies regarding SGBIs. Additionally, the Panel will discuss key long-term safety issues associated with SGBIs in the real-world setting for both the currently mandated studies and future studies for newly approved SGBIs.

So before I begin, I would like to ask our distinguished Panel members and the FDA staff seated at the table to introduce themselves.

Please state your name, your area of expertise, and your position. I would like to begin to my right.

DR. CROUCH: Morning. I'm Barbara Crouch. I'm a pharmacist and a clinical toxicologist at the University of Utah, College of Pharmacy.

DR. GLASSMAN: I'm Len Glassman. I'm a diagnostic radiologist, and I'm in private practice in Washington, D.C., also Clinical Professor of Radiology at GW.

DR. McGRATH: I'm Mary McGrath. I'm a plastic and reconstructive surgeon, and I'm at the University of California San Francisco where I'm a Professor of Surgery.

DR. HENNESSY: Good morning. My name is Sean Hennessy. I'm a pharmacist and epidemiologist, and I do drug safety research at the University of Pennsylvania.

DR. GALANDIUK: Hello. My name is Susan Galandiuk. I'm a colorectal surgeon at the University of Louisville where I'm a Professor in Surgery and Director of the Price Institute of Surgical Research.

DR. MOUNT: I am Delora Mount. I'm Associate Professor of Surgery in Plastic and Reconstructive Surgery at the University of Wisconsin in Madison, Wisconsin.

DR. VEGA: Hi. Buenos dias. Marlena Vega. I'm a patient advocate, and I'm a psycho-oncologist. I practice in New York, and I'm a third generation survivor and a three-time survivor of cancer.

MS. MATTIVI: I'm Kris Mattivi. I'm the Consumer Representative on this Panel. I'm a physical therapist and the Manager of Analytic Services at the Colorado Foundation for Medical Care.

MR. HALPIN: Good morning. I'm Mike Halpin. I'm a Vice President of Regulatory Affairs with Genzyme Corporation, which is now a Sanofi company, and I have a background in medical device, cell therapy, and gene therapy regulatory affairs.

DR. LoCICERO: Thank you. I would like to continue with Mr. Melkerson.

MR. MELKERSON: I'm Mark Melkerson, Director of the Division of Surgical, Orthopedic, and Restorative Devices. I am a biomedical engineer by training.

DR. MARINAC-DABIC: Good morning. My name is Danica Marinac-Dabic. I am a physician and epidemiologist and Director of the Division of Epidemiology at CDRH's Office of Surveillance and Biometrics.

DR. CONNOR: I am Jason Connor, biomedical engineer turned statistician. I work for Berry Consultants where I design clinical trials and also have an appointment at the University of Central Florida's College of Medicine.

MS. DUBLER: I'm Nancy Dubler. I'm an attorney. I'm Consultant for Ethics for the Health and Hospitals Corporation of New York City, and I'm Professor Emeritus of Bioethics at the Albert Einstein College of

Medicine.

DR. WHORTON: Hi. I'm Elbert Whorton, University of Texas Medical Branch, Professor of Biostatistics and Epidemiology. I'm semi-retired. I'm going back as the Director of Biostatistics at the University in the Galveston National Laboratory.

DR. LEITCH: Marilyn Leitch. I'm a surgical oncologist at UT Southwestern in Dallas. I'm a Professor of Surgery and the Medical Director for the Center for Breast Care.

DR. HONEIN: Peggy Honein. I'm an epidemiologist with the Centers for Disease Control and Prevention with expertise in maternal and child health epidemiology and birth defects epidemiology.

DR. CALLAHAN: I'm Leigh Callahan. I'm a clinical epidemiologist and outcomes researcher at the Thurston Arthritis Research Center at the University of North Carolina at Chapel Hill, where I'm a Professor of Medicine and Social Medicine.

DR. LoCICERO: Dr. Jones?

DR. JONES: Elizabeth Jones. I'm a radiologist and Director of Clinical Operations Radiology, Clinical Center, NIH.

MR. SWINK: I'm James Swink. I'm the DFO for this meeting.

DR. LoCICERO: We have a couple of individuals who are not present.

MR. SWINK: Dr. Blumenstein and Dr. Ewing were scheduled to

be here for the last two days. They both had personal conflicts and were unable to make it. So if you would, adjust your seating chart and --

DR. LoCICERO: Thank you.

If you have not already done so, please sign the attendance sheets that are on the tables by the doors.

Mr. Swink, the Designated Federal Officer for the General and Plastic Surgery Devices Panel, will make some introductory remarks.

MR. SWINK: The Food and Drug Administration is convening today's meeting of the General and Plastic Surgery Devices Panel of the Medical Device Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Sections 208 and Section 712 of the Federal Food, Drug and Cosmetic Act are being provided to participants in today's meeting and to the public.

The FDA has determined that members and consultants of this Panel are in compliance with the Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to

special Government employees who have financial conflicts when it is determined that the Agency's need for the particular individual's services outweighs his or her potential financial conflict of interest. Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special Government employees and regular Government employees with potential financial conflicts when necessary to afford the Committee essential expertise.

Related to the discussion of today's meeting, members and consultants of this Panel who are special Government employees have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses and minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss and make recommendations on postmarketing issues related to silicone gel-filled breast implants. The discussion will include different innovative methodological approaches to the conduct of postmarket studies and key long-term safety issues associated with silicone gel-filled breast implants in the real-world setting. This is a particular matters meeting during which specific matters related to silicone gel-filled breast implants will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208 and Section 712 of FD&C Act. A copy of the statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Michael Halpin is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Genzyme Corporation.

We would like to remind members and consultants, if the discussions involve any other products or issues not already on the agenda for which the FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the Panel of any financial relationship they may have with any firms at issue.

For the duration of the General and Plastic Surgery Devices Panel meeting on August 30th and 31st, 2011, Dr. Leigh Callahan, Dr. Barbara Crouch, Dr. Elizabeth Jones, Dr. Sean Hennessy, and Dr. Marena Vega have been appointed as Temporary Non-Voting Members.

For the record, Dr. Callahan serves as a Consultant to the Arthritis Advisory Committee of the Center for Drug Evaluation and Research. Dr. Crouch and Dr. Hennessy serve as consultants to the Drug Safety and Risk

Management Advisory Committee for CDER. And Dr. Marlena Vega serves as a patient representative to the Oncology Drugs Advisory Committee for CDER. Dr. Elizabeth Jones serves as a consultant to CDER.

These individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

This appointment has been authorized by Jill Warner, J.D., Acting Associate Commissioner for Special Medical Programs on August 29 of 2011.

Before I turn the meeting over to Dr. LoCicero, I just have a few general announcements.

Transcripts of today's meetings will be available from Free State Court Reporting, Incorporated. Telephone number, (410) 974-0947. Information on purchasing videos to today's meeting can be found on the table outside the meeting room.

The press contact today is Erica Jefferson.

I would like to remind everyone that members of the public and press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the Panel meeting is concluded.

If you are presenting in Open Public Hearing today and have not previously provided an electronic copy of your slide presentation to the

FDA, please arrange to do so with Ms. AnnMarie Williams at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time you speak.

And please, finally, silence your cell phones and other electronic devices. Thank you.

DR. LoCICERO: We will now have a recap, a brief recap, of Day 1 from Dr. Cara Krulewitch, Branch Chief of the Division of Epidemiology in the Office of Surveillance and Biometrics of the FDA.

I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

You may begin when you're ready.

(Pause.)

DR. KRULEWITCH: Thank you.

Technology can sometimes be our friend and not.

Before I go on, I wanted to make sure to acknowledge all of the hard work that was done by a very large working group that has been gathered together for well over a year, working on not only preparation for this Panel meeting, but also in preparation for many of the documents that you've seen on the website since January and continuing to June that have been with -- actually, just about every office in our whole center has worked

on this. There have been representatives, and I wanted to make sure that they all got acknowledgment here for their hard work.

Just to recap and go back to the discussion that we had yesterday, the primary focus of this study is to really consider where we're at now and what we want to consider for the future. So I'm putting this slide up again, where we kind of ended yesterday, that talks about some of the ideas and considerations to be thinking about today in your deliberations.

First of all, to explore some of the potential additional retention strategy, some of which was discussed yesterday, including involving other physicians and other primary providers and perhaps more novel approaches to patient reporting mechanisms for current studies.

Leveraging data, particularly from existing registries and other forms of information and literature that are out there as we go into the future with statistical modeling, simulation studies; considering how to power studies for more common endpoints. Considering also, perhaps, that maybe one study isn't going to do it all, that there may be more than one study, perhaps a number of studies, each to address different endpoints, which was talked about yesterday; and also, some of the methodologies that we're going to be using for some of the more rare events.

There was a question yesterday about demographics, so I have pulled off the most recent demographics from the American Society of Plastic Surgeons website where they have noted, in 2010, there were 296,000

implant surgeries for augmentation. That is for silicone and saline combined. They did also identify 50,559 silicone breast implant surgeries for reconstruction. And this is, for all cosmetic surgeries, the ethnic breakdown: 70 percent Caucasian, 11 percent Hispanic, 8 percent African-American, 6 percent Asian-American, and 5 percent other. And I stress that this is 2010, and this is taken from the American Society of Plastic Surgeons website. So this is probably some of the better data that we can find very quickly for you.

Really, I didn't have much more, as far as opening remarks, except to thank you for the hard discussion that you gave us yesterday and we're looking forward to much more of that today. I think that we have really gained a lot from the rich discussion that you have, and thank you for your work and time. That's it.

DR. LoCICERO: Thank you.

Does anybody on the Panel have questions for the FDA at this time?

DR. LEITCH: So I think yesterday, we were told the breakdown on the number of silicone versus saline augmentations was two silicone to one saline; is that right?

DR. KRULEWITCH: I don't know that it was two to one. I recall it may be a little higher, like 60 -- well, it's 60/40. Yeah. 60/40, 60 percent, 40 percent, I think. But let me double-check on that and get that for you again.

DR. LoCICERO: Ms. Dubler.

MS. DUBLER: Nancy Dubler. I have a question about conditions of approval. When the FDA approves something as safe, as effective with associated postapproval studies, that approval is not conditional on those studies, or is it?

MR. MELKERSON: Mark Melkerson. When FDA approves a study, it is approved for marketing within the U.S. The conditions of approval studies are used to augment the labeling to address some longer-term questions that may or may not have been addressed when they were shown to be relatively safe and effective.

MS. DUBLER: From my perspective, that's important. So even if it's clear that studies designed in the postapproval period will not produce the data that was once hoped for, that doesn't affect the underlying approval. That's correct?

MR. MELKERSON: As conditions of approval, it was pointed out that some of -- if you do not meet the conditions of approval, FDA does have regulatory authority to either impose civil penalties or other regulatory actions.

DR. LoCICERO: Dr. -- yes?

DR. MARINAC-DABIC: At the time of the approval, FDA certainly has a knowledge about the performance and safety and effectiveness of medical devices based on the short-term data. And the

reasonable assurance of safety and effectiveness is established based on the premarket data.

As Mr. Melkerson pointed out, there are still outstanding questions very often that has to deal, sometimes, with a longer-term performance, and that's one of the reasons why FDA can issue the conditional approval, but that's not the only reason. Very often, we do not have the knowledge how a device performs in the real-world setting and it is much broader in the patient population and much broader clinician population.

Very often, we have under-representation of certain demographic groups in the premarket data. So at the time when the reasonable assurance of safety and effectiveness is established, we certainly do not have knowledge of how a device performs in these groups, so that's a very legitimate question for the postapproval study.

In addition to that, many procedures involving devices are technically very complex, and sometimes the learning curve issue and learning curve effects are not studied in the premarket data. So that's a legitimate question for the postmarket study. Also, some safety concerns may be, you know, raised during the premarket phase, however, hadn't risen to the level of not really establishing reasonable safety and effectiveness. So we would like to look in a broader population to actually hone into a better understanding of what those might be, including also long-term effectiveness. All of these are legitimate reasons for asking for postmarket study.

So your question about what the FDA can do about the study that's not progressing and the study that does not yield the data that are useful or raise some concerns, there are many regulatory options we can use. Labeling options or changing the labeling certainly is an important piece, but one can only change the labeling when the study is really conducted well and data can be interpreted well. It's very dangerous to put in labeling something that's based on incomplete data or -- so again, that's one option.

We talked about yesterday about other more drastic options that the FDA can utilize, but I think at this point, it's important to know that, you know, there are many tools that we can use and better we define at this point what are still the gaps, what are the uncertainties, what are the areas we are needing to be stronger as the Agency and as certainly the Panel member can recommend. We will be working together with our premarket colleagues and our experts within the Center to make sure that we -- really, next steps are very comprehensive and yield to the useful studies.

DR. LoCICERO: Yes, go ahead.

DR. HONEIN: Peggy Honein. Can FDA provide any further information on these registries outside the U.S., like what sample size they have enrolled, what the racial ethnic diversity of their enrollments? I've seen the question a couple of times about how they might inform this, but I don't feel like I know enough about the enrollment at those registries to comment on it at this stage.

DR. MARINAC-DABIC: What we can do after the Public Hearing and for the discussion that will follow, we can provide the brief overview of these registries so you can have a sense what the potential of those registries might be for us in the future studies.

DR. HONEIN: Thank you.

DR. LoCICERO: Dr. McGrath.

DR. McGRATH: For the FDA, I need to be clear. As I understand, there were the core studies and then there's the large study. And one of the manufacturers yesterday said that they completed the 10-year core study with all the data and submitted it. And is it your -- is that correct that both manufacturers have, indeed, completed a 10-year course study, or is one completed and one almost completed and has that been to your -- has that met with the requirements for what you wanted for that 10-year study? I think that would help us, too, to know that.

DR. KRULEWITCH: We don't have that 10-year data yet. They mentioned they just completed it. They'll be submitting a report, and we need to evaluate that report very carefully before we accept it.

We have, to date, the eight-year data. So the answer is no, the studies are not complete from FDA perspective at this point, neither of them. The Mentor study is in the eighth year. We presented eighth year. We'll expect nine-year data coming in at the due date of the next annual report. So the answer's really no to that just yet.

DR. MARINAC-DABIC: And if I can only clarify the issue of completion. Even though the sponsors may consider some of the data collection being completed and the data submitted to the FDA, due to our review procedures, we do not consider a study is completed until not only we resolve all the issues from the final report, but also even if that's resolved, we keep the studies open on the public website, as I showed yesterday, until the company submits the labeling request based on the study data from the final report. So that has some difference in terminology under what we consider completed. So, again, to echo what Dr. Krulewitch just said, we do not consider these studies completed yet.

DR. LoCICERO: Dr. Hennessy.

DR. HENNESSY: We know that silicone breast implants sometimes rupture, and I've read about a concern of platinum in the silicone. Is there any assurance that there's no platinum in the silicone that we're inserting into women?

MR. MELKERSON: The most recent report from FDA on platinum, we'll get that to you this afternoon. I don't have the details in front of me, but the FDA did look into this platinum issue.

DR. LoCICERO: Dr. Mount.

DR. MOUNT: Just for clarification, did the FDA negotiate any benchmarking deadlines or particular timelines as far as completion on these serial updates for their 10-year study, both the core study and the large

study?

DR. KRULEWITCH: Do you mean when the reports are due or --

DR. MOUNT: No. As contingencies like if a certain benchmark of enrollment hadn't been made, that studies could be terminated or the company itself be in quite a bit of trouble. I mean were any specifics made as far as benchmarking?

DR. KRULEWITCH: We do have timelines. We do arrange timelines, agreed upon timelines with every study that we work on, including these studies. And as in my presentation yesterday, I talked about concerns of enrollment and that they were behind enrollment. And we will post that as a progress inadequate on our website. So there is that notation, and we pursue this as it depends on, you know, case-by-case basis with each study.

But because we saw the concerns with what seemed to be a delay in enrollment because they weren't meeting the timeline we had set, we started working with them. And if you recall yesterday, I had a slide that talked about some of the actions that we took with them and work with them to increase enrollment, which successfully got them to be able to complete their enrollment and enroll all the subjects that they had identified they would. So the short answer to that is yes.

DR. GALANDIUK: Are there precedents if a company does not fulfill their obligations, though, in terms of performing well on a postmarketing study? What things have you done in the past to discipline the

company, so to speak? Yeah. Or sanctions.

DR. MARINAC-DABIC: All right. So yesterday, we talked about all the actions that had taken place since we observed the slow enrollment rate. And what we typically do when we receive the report, certainly, there are several rounds of deficiencies being sent back and forth, putting together also the strategies for better enrollment. There have been documents that we have sent to both companies of the strategies that we, as the epidemiologists, know can improve the actual progress of the studies.

We typically have also, there are conferences requesting the progress. Companies had been actually very diligent in working with us, both of them. We also had face-to-face meetings with companies to make sure that if there are any clarifications needed to -- in terms of our positions are clearly stated. We also engage the Society of Plastic Surgeons, actually both societies, had the meetings with the leadership of both societies and presented in prominent panel sessions at annual meetings to actually try to get other stakeholders involved.

So these are more comprehensive strategies that we had done. They may not raise to the level of disciplining the companies, but again, it's our job to also better understand the obstacles and the real-world issues that the companies are facing when addressing these postmarket concerns.

Ultimately, the goal is to make sure that these studies are conducted, and you can take different approaches to get there. We have

chosen the approach that we wanted to advance the knowledge about these studies to engage the stakeholders that can help us to get there. And, certainly, you know, pressing the companies to change the procedures in terms of conducting the study, certainly, our efforts have not been fruitful to the extent that we would like them to be, and this is the reason -- and this is one of the rare studies when we have several thousands of -- actually tens of thousands of patients. So the challenges can be a little bit different than, for example, for other cardiovascular implantable devices where, clearly, there is a different risk-to-benefit ratio for some of those.

So this is why it's so crucial that we gain the unique knowledge that all Panel members can bring, what else we can do. We certainly have authorities, but if there are things that we scientifically and methodologically can do, we would be willing to build on your recommendations and then sit down again with companies and with all stakeholders involved, including the patient representatives to make sure that we get the best studies underway and inform not only the clinicians, but primarily the patients on those risks.

DR. LoCICERO: Mr. Halpin.

MR. HALPIN: When looking at approval letters for sponsors when they get approved, there's typically a -- there can be a large number of postapproval commitments. And I think what we're talking about today is specifically one clinical trial or one of those postapproval requirements, which is the PAS study. Is that correct in terms of where the enrollment has

not been kept up to speed with that? These sponsors are working on that, but also there are a number of other postapproval requirements that they're working on as well?

DR. KRULEWITCH: That's true. We're talking about one of many other items that might be in the letter.

DR. LoCICERO: Dr. McGrath.

DR. McGRATH: What approach have you considered? Although the 10-year core studies haven't been finalized yet, you've got eight or nine years, and the data that's coming in in those studies can deal with some complications that aren't so rare. So have you considered pulling those out of the large studies so that the large studies can be configured to really focus only on the very rare events which then would change the character of those studies because you would be looking for different things?

DR. KRULEWITCH: I think that you'll see in the questions we have later that we may want to hear some of that discussion from you. I think that you raise a question that I would save for later in the deliberations.

DR. McGRATH: Okay.

DR. LoCICERO: Dr. Marinac-Dabic.

DR. MARINAC-DABIC: If I may add to that, I think it is important. The question that you are raising is a really important one because our objectives of -- or the questions that still remain are still there. How we get to the responses of the questions is something that I think

deserves some other discussion during the afternoon or morning session, meaning that there might be different ways on how one can actually structure the study or studies in order to get the questions. So I think we are very open to creatively address the more frequent events in one set of scenario and the more rare events in a different scenario.

DR. LoCICERO: Dr. Jones.

DR. JONES: In postmarketing studies of some of the other devices, are there examples where all stakeholders have come together to really accomplish a really large study such as this? I'm just worried that this requires a lot of infrastructure, that it's hard for the companies to devote so much of their resources to really accomplish this, and really, you need to involve the patients and the physicians and perhaps other stakeholders to really, you know, make this happen. Are there other examples where that has been undertaken and that it was successful?

DR. MARINAC-DABIC: Well, this is definitely the largest study that we have ever asked any company or any companies to do, so there are no examples of this size and the scope of work that needed to be done. There are several examples of the ways how we have utilized the existing registry to nest the postapproval studies, meaning that there is the role of that entity, in addition to the sponsor.

INTERMACS is one of the examples that I talked a little bit about yesterday. Again, this is a registry for ventricular assist devices. Again,

the size of it is somewhat different, the population is somewhat different, but it still had set a precedent for engaging, you know, other Federal partners and other stakeholders and certainly redefined the sponsor in these type of studies.

For those of you who attended one of the cardiovascular panels that we had recently, you also heard the discussion about society stepping up to the plate, really talking about, you know, the roles that they can play in making sure that the registry is established that can actually be ready to accept many, many new device modules as they come to the market.

So there are many, again, other examples where we are in the process of moving toward the less traditional type of studies that will involve new data collection for the newly enrolled patients, but they're trying to leverage off the evolving registries, linking with other data sources, ways how we integrate that knowledge as the device is moving to the market.

DR. LoCICERO: Okay. Thank you very much for your presentation. We appreciate it.

We will now proceed to the Open Public Hearing portion of the meeting. Public attendees are given the opportunity to address the Panel in person to present data, information, or views relevant to the meeting agenda. Mr. Swink will now read the Open Public Hearing disclosure process statement.

MR. SWINK: Both the Food and Drug Administration and the

public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the Open Public Hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationships that you may have with any firm or company that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. LoCICERO: We have a number of public speakers today; therefore, I want to go over the process to ensure smooth transition from one speaker to another. And I would like to say that, unfortunately, I've been informed that I was too lenient yesterday, so we are going limit -- be very strict about your five-minute limit.

When you speak, a green light will appear. A yellow light will appear at one minute remaining. At the end of five minutes, a red light will appear and your microphone will be switched off. We're going to stick very

strictly to this. In addition, we are not going to allow speakers to read for anybody else. If you are planning to read for someone else, please submit your written comments to the table out front, the registration table, and those comments will be distributed to the Panel. In addition, if those comments are currently present on a website, please submit the website to the registration desk, and those information pieces will be distributed to the Panel.

If you are speaking for an organization, we would request that you also please state your mission statement. It can be one sentence and it can be paraphrased, but we want to know what your mission statement is for your organization.

The Panel is interested in your comments and wishes to understand the context of your comments. For those of you reporting case histories, we would like to know if you have been part of the studies that we are discussing today or if those problems that you are having were reported to the MedWatch program.

I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Chair. Please remember that the topic of this meeting is the future of postapproval studies for silicone gel-filled breast implants. We encourage you, the open public speaker, to stay within the realm of this topic, and I would remind you again to please state

clearly your name and your affiliation prior to presenting. Thank you.

Our first speaker is Dr. Dana Casciotti.

DR. CASCIOTTI: Good morning. I am Dana Casciotti. I am the Public Health Research Director at the Cancer Prevention and Treatment Fund. We are a nonprofit center that uses research findings to improve prevention and treatment strategies. Our nonprofit does not accept money from pharmaceutical or device companies, and I have no other conflicts of interest to report.

My perspective today is as someone trained in public health. I have a Ph.D. from Johns Hopkins University and a Master's in Public Health from the University of Pittsburgh, and I have previously worked at the National Cancer Institute. So I'm very familiar with clinical trials and research methodology.

You have already discussed how poor the follow-up was on the implant studies. I was disappointed that an FDA official implied yesterday that most of the postmarket studies were fine and only a few were not. I disagree. It was not just the Mentor large study that was so outrageous after only three years, and Allergan barely kept half of their augmentation patients after only two years; the adjunct studies were even worse. Only 16 to 23 percent of the women were still in the studies after 5 years. The core studies were slightly better, but Mentor had only 58 percent of patients at 8 years, and that is not acceptable at any of the places where I've done research.

Our nonprofit has talked to many women who have serious problems with their breast implants, and I'm not talking about patients from 20 years ago. I'm talking about more recent implant patients. But many of these patients have missed work because of their illnesses and couldn't take the time to be here today. Some told us their kids are going back to school this week and had to be at home for that. Others didn't hear about this meeting in advance. It wasn't exactly highly publicized to the general public, but history should be our guide.

We know that most knew breast implants seemed great at first. It isn't until years later that it becomes obvious that the newer, safer breast implants also break and leak and cause problems. So it may take a few years to get a better idea about the safety of the new cohesive gel implants, but we already know, after yesterday's testimony and from talking to many other patients, that these new implants can bleed silicone into the scar capsule even when the implant is intact. And even the new implants can break.

I also want to correct some misconceptions that were reflected in yesterday's Panel discussion. The large studies done by Allergan and Mentor are not asking women to come into their plastic surgeon's office every year. Most years, they're asking women to fill out a questionnaire which they can do online at home. I've seen copies of these questionnaires, and they are much too long. By the time women get to questions about their symptoms on page 22 of the Allergan questionnaire, for example, they will

have already answered about 20 connective tissue disease questions, many of which they have never heard of and can't pronounce, such as one called eosinophilic fascitis, which I'm not sure I can pronounce correctly either.

They will also have answered the same 20 questions about each of their children. I have to assume that by the time they get to page 22 to answer questions about symptoms they might actually have, they're in no mood to answer a question about dilated red blood vessels under the skin surface that appear as red marks, especially on the hands, face, and lips.

Given these questions, I think it's very unfair to blame the low response rate on the patients. Similarly, Mentor patients have told us that the symptoms listed on their questionnaire were often very confusing and difficult to answer.

And I have just one more thing to add. The first two years of the Allergan and Mentor core studies showed that self-esteem on the Rosenberg Self-Esteem Scale actually went down in most patients with implants and that symptoms of connective tissue disease went up. Those data were reported at previous FDA advisory committee meetings, but those data are missing from the analyses that the FDA has reported for the 8-year and 10-year core study follow-ups. I would ask the FDA to explain why.

Thank you for your time.

DR. LoCICERO: Thank you.

We have been informed that Sally Greenberg and Pamela

Bridgewater are going to be late. The next speaker will be Kate Ryan.

MS. RYAN: Good morning. My name is Kate Ryan, and I'm here today on behalf of Breast Cancer Action, a national education and advocacy organization that carries the voices of people affected by breast cancer to inspire and compel the changes to end the epidemic.

BC Action has over 35,000 members nationwide who believe that patients should come before profits. Breast Cancer Action has a formal corporate donations policy that precludes our accepting donations from any company that might present a conflict of interest, including all health industries, pharmaceutical and medical device companies, and any business whose products increase the incidence of cancer.

BC Action has been testifying at these meetings on behalf of women seeking safe and effective reconstructive surgery for many years. It has now been 25 years since FDA declared silicone breast implants a Class III device, and in that period, only weak attempts have been made to conduct sound research with adequate follow-up to assess the safety of these implants.

Even the two gold standard studies of the implants which form the bedrock of the Institute of Medicine's report on the devices have major shortcomings. The Nurses' Study was beset by conflicts of interests and dismissed women of major concerns as outcomes. The Mayo clinic study, likewise, did not examine systemic conditions, such as fibromyalgia as an end

point. Both studies openly acknowledge that despite their large sample sizes, they were not large enough to detect significant effects of the implants on low prevalence outcomes.

We are very pleased that the FDA is beginning to postmark its surveillance seriously, particularly for products that were approved on the condition that the manufacturer complete Phase IV studies. We've reviewed the interim findings released in June provided by FDA with data from Mentor and Allergan on their SGBIs. Research by the two manufacturers provided possibly the best dataset on the devices that we have, given that they are prospective studies. Nevertheless, we had considerable concerns about the inability to maintain participation in the studies and the shocking incidence of rupture and additional surgeries, particularly for women who have used the implants for reconstruction of their breasts following mastectomy.

Follow-up rates in the two large studies are dismal. Nearly 80 percent of the women in Mentor's large study then lost to follow-up after only 3 years. Given that these studies were a condition of approval, Mentor should have done much more to ensure it had the technical skills to locate women and provide women with incentives to continue participation in this important research. Geographic relocation should not be the hurdle it once was given the availability of the internet to find individuals and contact them.

Although Allergan's follow-up rates in their large study are also disappointing, they look considerably better when compared to those of

Mentor, and an examination of the differences between the two company's approaches should be able to discern their disparate follow-up rates. As it is, the available data cannot be considered valid with such skimpy returns and the potential for bias and dropout rates.

And, of course, 10 years doesn't capture many of the long-term risks when considering things like cancer. Rupture, reoperation, and removal rates are higher for women using implants for reconstruction than they are for women who are augmenting their breast size. This is not surprising given the age and health differences between the two groups and was well-known at the time that the devices were approved for marketing by the FDA. At that time and still, Breast Cancer Action thinks that these indications of device failure are far too high for the FDA to dismiss them by concluding that silicone gel-filled implants have a reasonable assurance of safety and effectiveness.

In general, the tone of the FDA's report was reassuring, but we don't feel the reassurance was evidence-based. For example, reoperations within two to three years of implantation approached 40 percent of participants in both core studies. Yet, the FDA summarized the finding by declaring that the majority of SGBI patients in the core studies did not require reoperation.

Little was mentioned in FDA's June report about this small study of physician-provided informed consent, but what is evident is the doctors are still reluctant to provide women with -- provide their patients

with easily available written information that may influence decisions whether or not to undergo breast implant surgery.

We appreciate the FDA's plans for oversight in these Phase IV studies and applaud their work with the companies to strengthen their research efforts, but we're skeptical that this will be enough to provide the needed information. In conclusion, Breast Cancer Action continues to believe that silicone gel-filled breast implants are ineffective and potentially unsafe as an option for reconstruction after mastectomy, and we urge you to recommend that the FDA reconsider their broad availability given the results of these studies.

Thank you for your time.

DR. LoCICERO: Thank you.

Our next speaker is Beatrice Ring.

MS. FAUCETTE: We had a video to show for Beatrice Ring, and there were some technical difficulties.

DR. LoCICERO: Okay.

MS. FAUCETTE: Mr. Swink said we could --

DR. LoCICERO: Please send -- if it's a YouTube video, make sure we have the link --

MS. FAUCETTE: Um-hum.

DR. LoCICERO: -- and we'll allow everybody to see it later. Thank you.

MS. FAUCETTE: Okay. All right. Thank you.

DR. LoCICERO: Next speaker is Susan A. Pope Helman.

MS. POPE HELMAN: Hi. I'm from Gatlinburg, Tennessee, and in the chair over there, I have all the meds I'm taking right now. I have reported to MEDLINE several times, many times. I'm here to address the question of postmarket long-term safety studies and issues resulting from SVIs. I wrote a book, now in second edition, which included interviews with more than 50 women and was based on over 250 women, all different yet all suffering with similar illnesses, just different levels of disease directly related to the gel in breast implants.

The eventual rupture of the implant allows this gel to travel throughout the body and even cross the blood-brain barrier, and once it's in the body, there's no way to get it out. The long-term exposure to the chemicals and microscopic heavy metals in silicone gel implants causes debilitating acute and chronic symptoms, similar but not identical to the symptoms of diseases such as MS, lupus, chronic fatigue, fibromyalgia, rare lymphomas, multiple neuropathies -- excuse me -- multiple chemical sensitivities. In fact, research has clearly shown an increase of giant macrophages after breast implants are in the body.

Long-term is important here because I was not diagnosed with Raynaud's or Sjögren's until over 11 years after implantation. My diagnoses stand as silicone gel-induced disease processes and silicosis.

We, the women who have been guinea pigs for plastic surgeons and manufacturers, have never had the opportunity for informed consent because of the lack of objective, long-term scientific data. When women with implants tell their doctors about their health problems, they're treated as hypochondriacs. We've been told by most doctors that our health problems could not possibly be related to our implants; yet, many of us do get better when they're removed.

Silicone gel breast implants provide a very comfortable income for plastic surgeons and the manufacturers. FDA requires the implant manufacturers to conduct long-term research, but there are two major problems with the research. Number one, FDA did not do a good job of making sure the studies were well designed so that even those that are completed lack some of the most important information about health effects. FDA did not seem to care that the manufacturers did not want to measure the increase of autoimmune symptoms instead of evaluating the symptoms that are most strongly associated with silicone gel implants. FDA allowed the companies to focus on the diagnoses of connective tissue diseases, most of which are rare. These kinds of diseases are diagnoses after years of symptoms so that 10-year studies are not long enough.

Number two, in most of the studies, the companies lost track of the patients early on. What happened to these women whose implants were removed? It seems that in most cases, they were removed from the studies

so that the very women whose problems were most severe are not included in the studies. The manufacturers and the plastic surgeons helping with the studies were happy to focus on the women who had no problems with their implants. This has biased the results.

My implants ruptured and have been removed. However, I still have silicone that has crystallized in my saliva, my mucus, urine, blood, and my eyes, ears, and nose also ooze crystallized silicone. As a direct result from the chemicals and heavy metals used to manufacture silicone gel breast implants, I suffer daily with the symptoms of MS, lupus, visual problems, fibromyalgia, multiple chemical sensitivities, severe migraines, peripheral neuropathies, connective tissue disease, and demyelinating lesions in my brain.

The remaining capsules, tissue, lymph nodes, and three bone marrow samples, and foreign materials found upon subsequent surgeries over 11 years after implantation were sent to the pathology lab of Dr. Nancy Hardt at the University of Florida Department of Pathology, as well as a forensic toxicology lab in Houston. These samples were found to have extreme high levels of silicone polymers, platinum, and foams found in a silicone gel in my very implants.

These levels of residual silicone gel in my body are most definitely causing my illnesses. I've been told that I can't even donate my organs because of all the silicone polymers and platinum in my tissues.

I hope the Panel will make sure future studies of breast implants include the most important questions regarding health risks and --

DR. LoCICERO: Thank you.

Our next speaker is Sharon Schwengler.

MS. SCHWENGLER: Good morning. My name is Sharon Schwengler, and I'm from Phoenix, Arizona. I'm here on my own accord, and I have not been compensated by anyone. I'm here because I'm sick from my saline implants. However, I understand your focus is on silicone, but since the companies are doing research to compare the risk of silicone gel implants to saline, I feel you need to know that saline implants can cause serious health issues too.

I was implanted in 2005 and explanted two months ago. Before getting implants, I asked my plastic surgeon what complications could occur, and he simply said capsular contracture or they would rupture and leak, and if they ruptured and leak, it would simply be saline water that filled my body. And if I had capsular contracture, they would simply remove the implant.

I also asked him -- I was smart enough to ask this because what happens when water just sits in a dark, moist area -- if mold or bacteria could grow. He said absolutely not because it was a sterile, enclosed environment. I asked of my plastic surgeon about all of the women who had filed lawsuits who said they had immune disorder issues from their implants, and he said studies had shown that those women had predisposed medical issues and

that those were silicone implants and these were saline; therefore, they would not harm me.

He also never told me that the outer shell of my implant was silicone. If I had known that the outer shell was silicone, I wouldn't have gotten my implants. If I had known I would have gotten sick, I wouldn't have gotten my implants. He also never told me that if I had to have them removed, that my breasts could look deformed. That would have been something I would have liked to known. I have been told that there are pamphlets that were supposed to be given, that the FDA recommends to be given to each patient. I never even saw that pamphlet.

Before my implants, I ran three marathons with the Leukemia Lymphoma Society to find a cure because I had lost a friend. I'm going to try not to get upset here. But I ran three marathons, four halves and many 5K's and three to four years after getting my implants, I could not run anymore. I got very sick. My hair started coming out. I had many, many issues with even hiking because my hips and joints, my neck, my back. My doctor tried to say I had fibromyalgia and what is that -- what the heck is that anyway? What is fibromyalgia? And after I got my implants removed, three days after, I didn't have those aches and pains anymore. That was just two months ago.

One of the major issues I had is *Candida*, and it was showing up in my blood, and that's a pretty dangerous thing, from what I was told. Thank God it's not showing up in my blood anymore. I missed a lot of work, and

thank goodness I work for a fabulous company because they worked with me. When my implants were removed, they found *Aspergillus niger*, and they also found *Candida* in my implant. I am 80 percent better, thanks to God, thanks to God because no one else would help me. And I spent over $32,000, including my explant surgery, in the past two years, and doctors were telling me nothing was wrong with me, nothing was wrong with me. $32,000, delved into my 401(k) twice to get better, just to get better, and I only thought my implants would cost $6,500.

I don't know how often these kinds of health problems are caused by breasts implants than the others, but guess what? I don't think anyone else here does either. The reason we don't know is because the studies have asked the wrong questions. I don't think this is coincidental. I think, when implant companies and plastic surgeons pay for or conduct studies on breast implants, they ask questions which make implants seem safe.

I am here to say it is time to find out what the real risks are of breast implants, including saline and silicone gel implants. Meanwhile, if doctors think that the problems I had are rare, just a little bit rare, they should -- it should be mandatory that they tell their patients. I mean why isn't there a warning label on breast implants like there are any other pharmaceutical drug or medical device out there?

I know the truth based on my experience and also because I

have talked to many women on different forums because after I found out I was sick from my implants, I went searching for the truth. And there are over 3,200 on one and 4,200 on another who continuously -- every day, there are people joining, and they're continuously getting sick. Almost all the women had similar stories.

I plead with you to not ignore this growing epidemic of women with aging implants and serious health problems. Not everyone gets sick, but those of us who do, we pay dearly.

Thank you for your time today.

DR. LoCICERO: Thank you.

Our next speaker is Dawn Alcott-Miller. Okay. That one is out. We're going to ask questions at this point.

Ms. Schwengler, if you wouldn't mind coming back? And just tell us if you have reported your problems to the FDA MedWatch. We realize it just happened. If you have not, are you planning to report?

MS. SCHWENGLER: No, sir, I have not, but quite honestly, would it have made a difference? And the only reason why I ask that is because my plastic surgeon told me nothing was wrong with me and I had ten other doctors I went to who told me --

DR. LoCICERO: I'm sorry. You have trouble now. Are you planning to report?

MS. SCHWENGLER: Yes, sir. If you think it will make a

difference, I will.

DR. LoCICERO: I understand that the FDA wishes to ask a question of Dana Casciotti.

DR. MARINAC-DABIC: Hi. Thank you. I just would like you to restate your specific question so we'll be able to address it later during the day.

DR. CASCIOTTI: I specifically wanted to know why the data about the self-esteem and the connective tissue symptoms were missing from this advisory committee meeting and the report, where they were previously reported.

DR. MARINAC-DABIC: All right. Thank you.

DR. CASCIOTTI: Thanks.

DR. LoCICERO: For Ms. Ryan, can you tell us the number of members in your organization?

MS. RYAN: Breast Cancer Action has over 35,000 members nationwide.

DR. LoCICERO: Thank you. Any other questions?

Okay. We're passing around the platinum report now.

DR. CONNOR: Can I ask a quick -- Ms. Casciotti, can you state the citation for -- you mentioned the self-esteem numbers going down that you had seen before -- and I just wondered where that was.

DR. CASCIOTTI: I don't have that with me, but I can get it for

you.

DR. CONNOR: All right. I mean is it published? It was in previous FDA materials at a previous panel or --

DR. CASCIOTTI: Yeah.

DR. CONNOR: Okay. Thanks.

DR. LoCICERO: Thank you.

Our next speaker is Mary Rosser Furr.

MS. ROSSER FURR: I'm Mary Rosser Furr, and I have no conflicts.

I came to this meeting with a different story; however, the outcomes we have experienced are similar. I was born in 1961 with a cleft lip and cleft palate anomalies and experienced several different procedures to correct the anomaly itself and the facial deformities that went along with that.

When I was in my mid-20s, I had several other maxillofacial surgeries. The first of these procedures in 1985 included a silicone gel chin implant and silicone cheek injections. The surgeries were successful, and I was pleased with the outcome. My surgeon was intelligent and competent and well-trained. I was a health and physically active and happy with my life, building my career and taking college classes.

In 1988, still in my 20s, I began to experience pain in my knee joints and found it difficult to walk up and down hills, steps, and slopes. I

could not walk fast, often feeling like I was walking in quicksand. At times, I relied on a cane to help walk, and from there, a long list of symptoms that seemed not to be connected to each other or point to any one health condition. Most of my basic living activities became harder to complete. By the mid-1990s, I was deemed too disabled to be rehabilitated for work and/or college and skill training.

I had cognitive dysfunctions, seizures, peripheral neuropathy, extreme, debilitating fatigue, balance and coordination issues, and problems with manual dexterity, sleep disorder, and pain. In each of these syndromes and disabilities, there are multiple symptoms that create obstacles in work, life, daily living skills, social activities, and other daily tasks. I believe that none of this would have happened if it had not been for that one, small silicone gel chin implant and silicone gel injections.

The explant surgeon who replaced my silicone chin implant with titanium medal in 1998 determined that it was the silicone gel-filled implant that caused many of my health problems and set off an autoimmune reaction that manifested in many different ways. Retsch Engineering, Inc., which analyzed my implant after it was removed, concurred. Having the explant surgery saved my life. However, it was too late to stop the cascade of disease and long-term disability. I have been able to rebuild my life and restore some of my health. I live with what I now call a new normal.

Networking with other implant survivors, I receive calls from all

over the U.S. from people who have facial implants who are experiencing several, multiple health problems. They were looking for a safety net, an answer to their health issues and reassurance. I could only listen. I had nothing to offer, but with the FDA's help, there may come a time where there is support in the way of information sharing between doctors, patients, and the corporations. And, in turn, the choices people make will result in healthy outcomes and productive lives.

I do not believe that all of my health problems are the result of silicone. Yes, some of my health problems have a genetic origin, but I am not the only person with facial anomalies. People like me, like people with a family history of autoimmune disease, need to be included in studies of silicone implants. Past x-rays have shown that my facial structure was in a slow, progressive, degenerative state. Fortunately, however, like breast implant problems you have already heard about, this seems to have reversed itself after explantation.

Today, you are hearing the individual stories to merely silicone survivors. Collectively, we share a common bond. We chose without informed consent to place silicone implants in our bodies. The results have often devastated our lives and livelihood and strained our family and friends to the breaking point.

Clearly, doctors are not informing patients of the serious risk of silicone implants, including autoimmune disease. There needs to be a clear,

written, black box warning that addresses all health risks, and those risks can only be determined by independent research studies.

DR. LoCICERO: Thank you.

Our next speaker is Sybil Niden Goldrich. Not here. Our next speaker is Jenny Kelly.

UNIDENTIFIED SPEAKER: Ms. Goldrich is just recovering from surgery. Can I read her --

DR. LoCICERO: No. Submit it to the registration desk, and we'll submit it to the Panel. Thank you.

Jenny Kelly?

MS. KELLY: Hello. My name is Jenny Kelly. I am speaking as an individual, and I am not affiliated with any organization or have accepted any payment for my expenses. I'm here to: one, show you an example of the differences between saline and silicone, what can happen; and two, some of the issues that arose for me.

I'll give you a brief history. I was implanted in June of '05, smooth, round saline manufactured by Allergan, inserted through axillary incisions. I was very fit, no prior medical conditions, no family history, all current family very healthy.

Let's see. I started getting symptoms approximately one year after surgery, started with large patches of hair loss and knee problems. I was a runner prior to my implants. I gave birth to my first child in December

of '07. I started to breast-feed. I immediately had left wrist pain, a left temple throbbing, and vertigo. I continued to breast-feed for four months until I could no longer withstand the illness and the chronic breast infections.

In May of '09, I breastfed again. I had my second child, who I breastfed for seven to nine months. By 2010, I was sick about every two weeks, on constant antibiotics, and I started seeking help, searching for physicians and trying to find the source of my infections, but it wasn't until 2010 that I realized how sick I was and that the infections weren't going away. Some of the symptoms were frequent urination, back pain, fatigue, wrist pain, temple pulsing, pelvic inflammation, wounds that were slow to heal, weight gain, and I had changes in mental status.

Last Christmas, my symptoms progressed, and by January, I could barely walk or lift my head. I had a sudden onset of -- arthritis, purple rashes across my joints, calf weakness, loss of short-term memory, no energy, severe inflammation, ovarian cysts, red rashes across my chest, on my neck, ulcers on my tongue which later became frequent, shortness of breath, hypersensitivity to sound and light, anxiety, tightness of skin, sudden food allergies, eye complications, neurologic issues, joint issues, external fungal infections, enlarged thyroid, and I developed grey-rimmed painful lesions in my tissue. And just to give you an example of how sick I was, I could not -- no longer lift my children. I could not stand the sound of their voice. I could no longer spell, nor do basic math. This was just this past winter.

I got tested. I was negative for all autoimmune diseases. My husband, who is also a physician, spoke to a surgeon who suspected fungal-related illness from my implants, so he put me on antifungal, and immediately, my condition improved. It was just a few weeks prior to surgery that I realized if I did not disturb my breasts, that I did not become ill.

So I had my implants -- I flew out to Georgia and had my implants removed on the 1st, and with that, we found I had enlarged and painful lymph nodes. Both implants were filled with more fluid than when they were originally inserted. Both implants were heavily colonized by *Aspergillus niger*, *Aspergillus fumigatus*. I had MRSA in the right capsule. Some cultures in the fungus were still 11 by 9 millimeters even after one month post-surgery. The large clusters were visible immediately upon removal. The MRSA, of course, spread after surgery, took me three rounds of antibiotics to clear it. Apparently you become very -- you can become resistant to antibiotics easily because you have this pocket inside you with fluid going in and out.

Since my surgery -- I'm sorry. I saw an infection disease doc who put me on voriconazole, which helped greatly. It even turned my nipples from black to brown within a week, a problem I didn't even know I had. I'm on itraconazole indefinitely through one of my physicians through Southwestern right now, and that's working out well, but since my surgery, I grew a painful axillary mass. I have had some setbacks, but I have improved

greatly. All of my autoimmune symptoms are gone. The majority of my anxiety is gone. I still get some infections, but they're very mild. The left wrist pain which I had since '08 is completely gone, but now I suddenly have severe --

DR. LoCICERO: Thank you for your presentation.

Our next speaker is Lana Merriam. Lana Merriam is not here. Next speaker, Beth Schaffer. Beth Schaffer is not here. Next speaker, Dr. Dennis C. Hammond.

UNIDENTIFIED SPEAKER: If I may, Mr. Chairman? Speakers, if you could remain six or eight inches from the microphone, it'll make it a lot clearer for our transcriptionist, please. Thank you.

DR. HAMMOND: My name is Dennis Hammond, and I'm a board-certified plastic surgeon in Grand Rapids, Michigan. I'm an Associate Professor of Surgery at Michigan State University, and I serve as the Assistant Program Director for our plastic surgery residency in Grand Rapids. I've been in practice for 19 years, and my travel today is sponsored by the American Society of Prosthetic Plastic Surgery, and I also have a consulting agreement with Mentor Corporation. Actually, I serve as a Medical Director for their CPG Cohesive Gel Study.

My practice is nearly completely devoted to plastic surgery of the breasts, and my practice mix is fairly evenly distributed between reconstructive breast surgery for women recovering from cancer as well as

cosmetic breast surgery. And because of the nature of my practice, as well as my academic involvement within the societies in plastic surgery, I've really been involved in nearly every study that's come down the pike here for the last 12, 13 years, including the core and adjunct from both companies, as well as the 410 and the Mentor -- now the CPG and the Mentor PAS. My involvement at the Mentor PAS level at this point now, at one year, we've been able to demonstrate a follow-up rate of 76 percent.

And so now, while the focus of this Panel is to look at those studies, I would like to clarify several of the comments made previous to this. I would ask your indulgence.

The first involves the safety and efficacy of these devices. Certainly, back in the early '90s, I think all of us were caught a bit off guard by the claims that were made, but since that time, more than 26 studies, depending on who you talk to, have been published in the peer-reviewed scientific literature, including the Institute of Medicine report, and there has been no associations between silicone gel implants and connective tissue diseases, including scleroderma, systemic lupus, rheumatoid arthritis, and fibromyalgia. And this experience is well documented in complete experience, provides a compelling contrast to anecdotal reports such as we're seeing today.

The second involves the informed consent process. Although every surgeon conducts that process depending on their own practice

patterns, in my hands, that's easily an hour-long event, and it's geared towards providing a full understanding of all of the potential risks and benefits. And this document that's been provided to us really is an extensive document. It covers all aspects of silicone implants, and it includes information as well on the current literature, and we're required to sign that when we complete the consultation.

Now, while the current PAS survey is exhaustive and it does address every condition suggested in the pre and postapproval studies regarding silicone gel implant, and while that may have fewer enrollees than expected, it should be remembered that the current core studies also provide much of the necessary information that we're looking for. In fact, the Mentor core gel study documented an 88 percent follow-up at three years, and that data has actually been studied, peer reviewed and published. And I would like everybody to keep that in mind as we go forward with these various studies.

My personal involvement with the Allergan core, I had a 94 percent follow-up at 1 year and an 89 percent at 5 years, and in the 410, I've had 98 percent at 1 year and 84 percent at 5 years. So we're really making a concerted effort to follow these patients up. These are robust studies, and I think that ultimately they'll provide very useful information that are really going to help us with regards to the issues we're talking about today.

And if I could just go forward, the importance of this effort

can't really be overstated. Sometimes, I think we get a misconception of breast augmentation. This patient that you see right here had got a well-recognized deformity called tuberous breast, and you can see there's deformity in the size and the shape of her breast. And for a young woman like this, it's easy to understand why her body image could be severely affected. Matter of fact, I remember interviewing with her and her mother. She was devastated by this condition.

This is her appearance postoperatively, after the placement of smooth, round silicone gel implants. Her quality of life, her self-concept and overall outlook had been tremendously improved as the result of an intelligent, responsible use of these devices. We simply have to keep women and patients like this in mind as we move forward with these devices to ensure timely and appropriate treatment options for treatment like this.

In the future, it seems that streamlined patient requirements, along with compensated time on the part of the patients, may be deciding factors in encouraging patient follow-up in breast implant studies. This, along with an involved -- this is one of the most important parts -- dedicated surgeons and study coordinators should provide the level of follow-up needed to develop meaningful data concerning the performance of breast implants.

Thank you for your time.

DR. LoCICERO: Thank you.

Our next speaker is Audrey Sheppard.

MS. SHEPPARD: Good morning. My name is Audrey Sheppard. I reside in Chevy Chase, Maryland. I'm speaking for myself and will be exceedingly brief.

In 1994, I joined the just-created FDA Office of Women's Health as its Deputy Director. A year later, I became Acting Director and served in that capacity from 1995 to '99. I am neither a professional health practitioner nor a scientist, but rather a women's health policy and communications advisor. As an independent consultant, at present, I do some work with small companies that are developing products to fulfill unmet health needs of women. One of these companies with which I have a de minimis relationship has developed an investigational device which would improve the procedure or process of tissue expansion after breast cancer surgery to facilitate the introduction of an implant.

My work with the FDA, which included an all-important FDA ruptures study being carried out on my watch, and my current work are entirely consistent with my longstanding position that breast implants must be manufactured safely to the highest possible standards, that more, not less information be available for women to have truly informed consent and that the FDA use its regulatory powers fully to enforce robust postmarket surveillance.

Because my time today is short, I want to put my perspective in

clear, bottom-line lay terms. I know this is a highly complex topic. I sat through many, may briefings that were way beyond me, so I commend you knowing you all have the expertise, but the subject can be made overly complicated as well. It comes down to this, that these devices were put on the market conditioned upon the performance of substantial follow-up studies. FDA is asking the right questions now about current and future studies, how to enhance them, make them more robust and, thus, more meaningful, more valuable to future women as they face the question of what to do after breast cancer.

I urge you to follow the science by insisting that future studies be well designed and well executed. Women are depending on FDA to get this right. Thank you.

DR. LoCICERO: Thank you.

Our next speaker is Ann Pugh.

MS. PUGH: Good morning. Thank you for hearing. I am here representing myself. I have no disclosures, no financial interest.

My name is Ann Pugh. I am 35 years old. I am a mother of three children, twins and another child, and also a wife. I decided a couple years ago, I was thinking about it for a long time, to have breast augmentation, and the decision was made more based on having the three children, breastfeeding three children, carrying twins. Things definitely weren't as they were before that time. So I was looking for just getting back

to the same breasts I had prior to my pregnancy and prior to my nursing.

I did some careful research, chose a very well-trained, great plastic surgeon, and decided to have the augmentation. Before having the augmentation, I had lengthy discussions with my surgeon related to the risks, the complications. I received written information. I had at least a one-hour consult for my first visit just to go over the saline versus silicone, what the implant risks would be, what the possible complications may entail, and also the suggested follow-up from the FDA related to MRIs and so forth.

Based on all the different information and literature I received, as well as other patients and women that I knew who had had prior procedures, I did decide to have the silicone gel implants about 18 months ago, and I will say, I have not regretted it a day since. I've had a very positive experience, had no complications. I do realize I am certainly only 18 months out, but I've had no problems with contracture, no issues, and looking in the mirror every day is certainly a much better thing for me than it was before. So just a realistic expectation to kind of get back to where I was before I had kids, and certainly, it's nice to be able to fit into clothes better and to feel more confident and have better self-esteem based on that.

So I do understand the risks still. I do plan to follow up with my surgeon if I do have any issues or any concerns. Probably, I will not choose to have routine MRIs based on the cost of the procedure, as well as the risk for false positives and unnecessary surgery based on the possible lack of a real

issue or complication.

So I don't have anything else to present, just a quick little personal statement. Thank you for your time.

DR. LoCICERO: Thank you.

Our next speaker is Dr. Garry Brody.

DR. BRODY: Thank you. I'm Dr. Garry Brody. I'm an Emeritus Professor of Plastic Surgery at the University of Southern California, Keck School of Medicine. I have been a past president of the American Society of Plastic Surgery, past president of the Educational Foundation, and past president of the Plastic Surgery Research Council. I've done a great deal of breast implant work, some of which I might share with you, most of which you know. I have written on safety and efficacy in several articles, which is in the published literature.

A conflict of interest: about 10 or 15 years ago, I was the medical monitor for the Mentor adjunct study, for which I did receive compensation, but I have not been involved with that in the last 15 years. I recently was invited by Allergan to do a five-city teaching tour about ALCL and breast implants. And because I am retired, I could not afford that much travel and I -- they did pick up all my expenses. I receive no personal compensation for it. I now have a grant to study ALCL from ASPS and for which I get no personal funding. All money goes to the study.

I would like to bring some perspective to this issue of silicone.

There is no one in this room who does not have silicone in their bodies. Every needle and syringe, every IV tubing has silicone in it, admittedly, very small doses, but if you look at a diabetic, a child with childhood diabetes, and follow the number of injections three times a day for years, for the rest of their life, they do get a heavy load of silicone. The only complication of that is they do get induration at the injection sites, and we know that it is injected silicone and it may be the insulin, I don't know, produces these indurated areas. There's no evidence, there's no literature that suggests that they have any other complications from what is a heavy load of silicone.

Secondly, it's now apparent that a broken implant with these new cohesive gels does not migrate beyond its -- either through the capsule or if there's an intracapsular rupture, it stays right there, probably forming a new capsule around it. I think, when you consider whether these should be removed, you have to weigh the risk of a ruptured implant and the gel versus the risk of a surgical procedure to remove it. The evidence, to date, suggests that that gel is nontoxic.

Finally, the pediatrician from yesterday talked about the lactation and all the silicone that's going into the baby. Well, I wondered whether -- he's not here today. I would have liked to have asked him if he ever prescribed Mylicon for infants who have colic. Mylicon is basically silicone, dimethylsiloxane, and it is an anti-foaming agent. It's available across the counter with no -- and apparently approved for use in infants. I've

also studied the question of whether there is silicone in mother's milk. I published, rather obscurely, I must admit, but we found no silicone in mother's milk.

Finally, I would like to emphasize some of the good things about breast implants. Women with breast implants are having less cancer -- approximately 30 percent less, multiple studies -- and also, when they do get cancer, the death rate is 30 percent late. These are studies done by Dennis Deapen and myself.

I thank you for your attention.

DR. LoCICERO: Thank you.

We would like to ask some questions of this cohort. Jenny Kelly, have you reported your conditions to FDA MedWatch?

MS. KELLY: I apologize for not addressing that earlier. I did report my illness to MedWatch, where I received an automated e-mail, and then Allergan did contact me within a reasonable time. They asked me what was going on, and I don't think I even got two sentences in, and they hung up the phone. Prior to that, I did tell Allergan that I was experiencing -- I was being -- I felt sick, and they told me to check out the FDA website. And then they also sent me a letter shortly after asking for their implants back.

DR. LoCICERO: Thank you.

Other questions? Yes?

DR. WHORTON: Does she happen to be in any of the Allergan

studies?

DR. LoCICERO: Were you in the study?

MS. KELLY: No, I was not.

DR. LoCICERO: She was not in the study.

Dr. Leitch?

DR. LEITCH: For Dr. Hammond. It seemed like you had very good luck with follow-up of your patients and mentioned a couple of things, that being coordinator and interested surgeon. Do you have a coordinator and what advice would you give these companies to facilitate retention of patients in study?

DR. HAMMOND: That's a great question because, as I showed you, I've been involved in these studies almost from the beginning, and at some point, while I think all of us want to have the data, you have got to reach a practical level of, can you do the study. And when all these patients come back to me, at this point, for me personally, it takes about half a clinic day to see all these people, and I have one secretary whose job is to make certain all of the paperwork is filled out, sent in, follow-up phone calls are made. It requires a significant effort and commitment to fulfill these requirements.

And even with that, I had some other data I was going to show you, but we studied the patients who didn't come back and what their reasons were for not coming back. And most commonly is because I don't

see why, I'm not having any problems, and we just couldn't convince them to come back and complete the study. So that's why I said at the end, you've got to have dedicated surgeons that are really interested in making this study work, and then they have to skew their office to incorporate that into their daily routine.

And then the other thing is, I think a really compelling part would be, if the patient has some sort of compensation, and it doesn't have to be wild really, just something that they get back to just compensate for the drive in. That helps a lot.

And I guess the recommendation that I would make is that, while it was certainly admirable to try to get 40,000 patients to come back, that just wasn't going to happen. You would be well served to utilize the tradition that all of us have in medicine, I think, and that's where we do studies, we report them, we peer-review them. That could function very well into the registry, the question that was asked earlier, that they have done so successfully in the Scandinavian countries.

So that kind -- and the other thing I was going to say is that if you can partner with physicians that are going to be dedicated to giving you this data and otherwise identify those offices that functioned particularly well, at the end of it, I think you'll be able to get data that will be useful.

DR. LoCICERO: Thank you.

We're trying to find the exact time of closure for enrollment for

these studies. Going to quickly get a date from the sponsors, approximate. Was it over 18 months ago?

DR. AVELAR: This is Allergan. For the core study, that started in 1999, took a year to enroll, closed in 2000. For the BIFS study, it started in February of 2007 and it took until March of 2010 to fully enroll.

DR. LoCICERO: Thank you.

Mentor, just closure and for enrollment of the PAS. Okay.

Then I need to ask Ms. Ann Pugh, are you a participant in either trial?

MS. PUGH: No.

DR. LoCICERO: Okay. You are not. Okay. Thank you.

Okay. Next speaker is Carol Ciancutti-Leyva. She's not here. Next is Caroline Glicksman.

DR. GLICKSMAN: Thank you. Good morning. My name is Dr. Caroline Glicksman, and I am a board-certified plastic surgeon. I'm an Assistant Clinical Professor at Jersey Shore University Medical Center, and I've been in practice for 20 years.

I'm presently an investigator for four clinical trials: the adjunct study since '98, the Allergan 410 CARE study since 2005, the Allergan breast implant follow-up study since 2007, and the Allergan Style 410 silicone study since 2008. I'm an educational consultant for Allergan, but I paid my own travel expenses and have received no financial incentive to be here today.

My community-based private practice has evolved over the last 20 years to be primarily breast augmentation and reconstruction, about 90 percent of my practice. I've published extensively on breast augmentation, but my primary focus is on patient education and informed consent. I've stood before this Panel twice in the last 10 years, expounding on the benefits of silicone gel implants and hoping that they be released back onto the market. My goal has always been to educate my patients, to obtain true, informed consent, to advance my surgical techniques and produce better outcomes for our patients, and to encourage long-term follow-up.

Although I applaud the FDA and this Panel's efforts to improve future postapproval studies, I'm really concerned that the members of this Panel do not fully appreciate the complexity of the requirements that exist in the current studies. They are, unfortunately, designed to discourage, not encourage patient enrollment and long-term follow-up. The first step in the current postapproval studies is patient enrollment. This is an issue preoperative patient education.

All breast implant patients in my practice are enrolled in either a clinical trial, a postapproval study, or followed systematically for as long as they have an implanted silicone gel device. I teach the importance of routine follow-up exams, and my patients enroll willingly in any study that I ask them to enroll in.

The result of this diligent follow-up over the last 20 years,

however, is that I am now seeing 12 to 16 breast implant patient follow-ups a week. The paperwork, the implant logs, the registry forms, the scheduling of follow-ups, and I have for an example here -- you can see what's up on there. I don't know if you can see it clearly. That is what I call a patient educator form. I spend approximately an hour with my patients on their initial consultation and make sure every single point is covered, from future mammography to future imaging to future possible surgery, to who has got the financial responsibility if the implants have to be replaced, to trauma, to breastfeeding. It's all covered before we even set up the possibility of a breast augmentation.

This, clearly, though, between this and the forms that patients then fill out -- this is just one page of the many forms when patients come in for routine follow-ups. We schedule the appointments 20 minutes in advance of their clinical consultation so they can sit and finish their paperwork. This becomes unsustainable in a private practice and has clearly become more a labor of love than a sound business decision.

The second critical challenge of the study compliance are the recommendations on MRI. Even my most educated, compliant patients either flat out refuse this requirement or simply cannot afford this diagnostic test. In addition, based on the current literature, suggesting that MRIs can produce a significant number of false positive reads and the low rupture rates seen with the form stable and the responsive gel implants, I strongly

advocate that these recommendations be modified.

I have been also following closely the studies and the recent ASERF study discussed yesterday that is utilizing high-resolution ultrasound to detect breast implant ruptures. I think this may be our future.

Patient compliance is the key and can only be achieved when physicians are committed to patient education, data collection, and most importantly, nurturing long-term relationships with their breast implant patients. The present study requirements place an undue burden on practices and their patients. When considering postapproval study designs, I urge the following:

Simplify the studies to encourage patients and physicians to comply and step into the 21st century. Develop web and telephone-based follow-up protocols that can efficiently screen large numbers of breast implant patients. Incorporate high-resolution ultrasound as a method of screening for ruptures, and consider the difference in rupture rates between the newer generation of silicone stable devices and the older generations when setting these guidelines for radiological surveillance. Patients simply cannot comply with the present MRI requirements. Finally, lift the restrictions on the use of Betadine. We want to see reduced revision rates, reduced reoperation rates, and the data supporting reduced capsular contraction with intraoperative Betadine use is robust.

Finally, set realistic, long-term follow-up rates. American

women do not get their annual mammograms, they don't wear safety belts, they don't get their pap smears. It is almost impossible for me to drag the patients back into my office with --

DR. LoCICERO: Okay. Thank you very much.

I would like to ask if Sally Greenberg has arrived. Has Pam Bridgewater arrived?

Our next speaker is Dr. Leroy Young.

DR. YOUNG: My name is Leroy Young, and I am President of the Aesthetic Surgery Education and Research Foundation. I have no conflicts related to this Panel hearing. My travel expenses were paid for the Aesthetic Surgery Society. The mission statement for ASERF is that we conduct and support clinical research. I'm a board-certified plastic surgeon specializing in clinical trials research, and I practice in Saint Louis, Missouri. I've been an investigator in the core study, adjunct study, and the PAS studies.

One of the things I want to emphasize is that there has been a lot of epidemiological work done, looking for a relationship between breast implants and connective tissue diseases, among other entities. And I am showing here examples of cohort studies that have been studied in peer review journals. This is additional cohort studies and then the conclusion of the cohort studies. There have also been a number of case control studies, and examples are shown here. These are more case control studies, and there have also been a number meta-analyses or structured reviews of this

same issue, and this is examples of those.

All together, there are at least 26 epidemiological studies and 13 meta-analysis or structured reviews that have failed to show a relationship between breast implants and a defined connective tissue disease, an atypical connective tissue disease, or a disease unique to breast implants.

Again, I want to emphasize the importance of registries, and these are examples of registry-based or data-based studies that have been performed in epidemiological studies. These are examples of the Scandinavian studies, which have provided some of the best evidence on complications and long-term outcomes. And, again, these were done in Scandinavia. Their current best data, I think, for rupture rates is, that is somewhere around one percent per year. And this is in the core studies for Allergan at 10 years, and it was 10 percent, and it was 13.6 percent at 8 years for the Mentor core gel study. There's also a large study in Sweden, published in *Plastic and Reconstructive Surgery* in 2006 that shows a rupture rate of 8 percent at 12 years.

Breast cancer has also been looked at in a series of studies in Scandinavia. Again, these studies highlight the power of registry and data-based systems. Similar studies have been done, looking at non-Hodgkin's lymphoma, including the Delong study which highlighted ALCL. Again, these have used registries or national databases. Suicide has the same profile. There are a number of registries out there, and I think what needs to happen

here is that we need to form a formal breast implant registry in the United States. I think it will give us the best data on rare diseases.

We now know, I think, that the main problems at least early that are associated with implants are local complications. The rare and unanswered questions require huge numbers of patients, and the best way, I believe, to get that is through registry data. So we agree with the FDA that, based on the totality of evidence, that breast implants are safe and effective when used as labeled. We also agree with the FDA that the benefits and risk of breast implants are sufficiently well understood that women can make informed decisions about their use. A U.S.-based breast implant registry should be established to facilitate detection of rare diseases and to establish a cohort for the study of unanticipated questions. Thank you.

DR. LoCICERO: Thank you.

Our next speaker is Dr. Phil Haeck.

DR. HAECK: I would like to thank the Panel for allowing me to be here and speak to you today. My name is Phil Haeck, and I am the President of the American Society of Plastic Surgeons. I am in private practice in Seattle, and I have no financial ties to corporations manufacturing breast implants. I have no other disclosures except that ASPS has reimbursed me for my travel today.

The mission of ASPS is to advance quality care for plastic surgery patients. ASPS has always taken a stand for patient safety. We want

the best for our patients, and we've been a leader in pursuing accurate outcome data that supports therapeutic decision-making by our members. Our patients directly benefit from the data we collect on surgical procedures and noninvasive injectable treatments.

To that end, given what we now know from the manufacturers' postapproval study dataset, the position of the ASPS is that the Panel should consider the following: The 2006 decision by the FDA to allow women to choose between silicone and saline implants has proven that both implants are indeed safe and effective. There's plenty of data to show that women have very high satisfaction rates from these devices. Greater than 90 percent reported met their expectations and improved their body image.

There has been shown to be no relationship between silicone breast implants and connective tissue disorders, which was the main reason these studies were agreed to on the release of these products. This issue seems to be settled with the PAS data as it already stands now. For women of America, this issue has been settled, and they continue to demonstrate their belief in the safety of silicone implants by now choosing them two to one over saline. In my practice, it's nine out of ten.

ASPS believes there are alternatives to get to the endpoints that were intended when collection of the PAS data was agreed to in 2006. The issue of capsular contracture and rupture rates can be concluded from many alternative data sources already in existence, especially when

combined with the volumes of data that PAS has already achieved. This alternative data sourcing can be used to verify and enhance the PAS data without the costly need to pursue women who have been lost to follow-up.

ASPS would strongly support that alternatives to costly and too frequent MRIs for women in the first 10 years of the study be considered. My colleagues have already offered additional testimony in regards to these alternatives. Too frequent MRIs at a cost burden of the patient are a significant impediment to getting all of the women of the study to what continues to be an ill-defined endpoint. Asking the implanting surgeons to track down happy and satisfied patients beyond one year of their operation will continue to be met with skepticism by them unless significant incentives are built in.

ASPS would like to help solve the problem of getting the follow-up data in the PAS more robust. We will continue to communicate to our members the importance of patient follow-up in these studies, but you've already heard that our patients and our members are busy, their time is important, and significant change in the incentive-base for this study will be required to change the loss to follow-up.

In addition, we strongly urge the Panel to focus on the known areas of concern for the postapproval studies, such as local complications. Postmarket surveillance, registries, case reports, and literature reviews are a preferred study design method for identifying rare events. The purpose of

the postapproval studies was to continue to evaluate risk of rare events and instance of local complications with particular emphasis on silent rupture.

I would submit to you that one of the key lessons learned from the PAS is that we tried to answer too many questions. Going forward, we need to be focused on the right questions and ensure that an appropriate infrastructure is provided to obtain appropriate data. The science has not identified an association between rare events like connective tissue disease and silicone breast implants. That question's already been answered.

My job, as a physician, is to help my patients make thoughtful decisions about whether breast implants are right for them. We believe that the body of scientific evidence provided by the FDA gives women the facts that they need to know to understand the issues and make informed decisions. We urge the Panel and the FDA to not simply extend the studies in their present form, but rather improve the studies by improving a way to make more robust postmarket surveillance data available. We would suggest epidemiologists from both the FDA and the manufacturers convene their own scientific meetings to this end, and we believe final conclusions can then be drawn. Thank you very much.

DR. LoCICERO: Thank you.

Our next speaker is Dr. Robert X. Murphy.

DR. MURPHY: Good morning. Members of the Panel, thank you for asking me to be here today and allowing me to present.

My name is Bob Murphy. I'm a board-certified reconstructive plastic surgeon and Program Director of the Lehigh Valley Health Network Plastic Surgery Residency in Allentown, Pennsylvania. I carry the academic rank of Professor of Surgery and have also received a Master's of Science Degree in Health Evaluation Sciences from Penn State University. I serve as the Assistant Chief Medical Officer at Lehigh Valley Health Network, and I am currently the Board Vice President of Advocacy and Health Policy for the American Society of Plastic Surgeons.

In my practice and as a Director of the Residency Program at Leigh Valley, I use both silicone and saline breast implants to treat patients seeking breast reconstruction after mastectomy and for the purpose of cosmetic breast augmentation. I have no conflicts of interest to disclose to the Panel today.

My travel has been paid for by the American Society of Plastic Surgeons, whose mission statement is to advance the quality of care to plastic surgery patients.

The focus of my testimony today will be upon the support that the American Society of Plastic Surgeons can provide to the collection of meaningful clinical data on breast implants through the national quality improvement and outcomes registry known as Tracking Operations and Outcomes for Plastic Surgeons, a.k.a. TOPS.

The American Society of Plastic Surgeons embraced the

important messages delivered by the Institute of Medicine's reports "To Err is Human" and "Crossing the Quality Chasm" by developing the TOPS program. Since 2002, the American Society of Plastic Surgeons has administered the TOPS registry as a HIPAA-compliant, secure and confidential national registry of plastic surgery procedures and outcomes. To date, there have been over one million plastic surgery procedures entered into this registry. Data from the TOPS registry has proven to be an invaluable tool for plastic surgery, playing an integral in numerous ASPS quality initiatives, including the monitoring of clinical outcomes and emerging trends and the development of evidence-based guidelines and practice parameters.

As a society, ASPS is always sensitive to patient care needs. For example, we formulated a venous thromboembolic events, VTE, initiative in response to the 2008 Surgeon-General's call to action regarding that particular national epidemic. Through the work of our research, patient safety and quality areas, TOPS data was utilized and analyzed to address important clinical questions related to VTE occurrence and patient risk factors and plastic surgery procedures. This resulted in ASPS developing robust clinical practice guidelines augmented by a national patient and physician education program. Additionally, analysis is currently being conducted to examine the incidents and types of complications associated with reconstructive and cosmetic plastic surgery procedures, including breast augmentation.

The TOPS registry program is a keystone element in ASPS' commitment to foster continuous quality improvement and measurement of clinical outcomes. ASPS member surgeons are able to enter their clinical case data and receive instant reporting and national benchmarking of performance. Recently, we expanded the registry to be able to collect patient reported outcomes related to breast surgery through the Breast-Q survey tool.

The TOPS registry can also serve as a valuable resource and tool for broadly collecting procedural specific and longitudinal outcomes data related to breast implant procedures. Currently through TOPS, our members can submit specific device and procedural information relating to their breast implant procedures.

As discussed during yesterday's session, ASPS is currently working in partnership with the FDA to develop a national registry on confirmed cases of ALCL in patients with breast implants. In the future, these data fields could easily be expanded and/or refined to facilitate and formalize data collection for the purpose of developing a national breast implant registry. This national registry could be designed for potential integration with other international breast implant registries or studies to aid in global data integration for analysis. We believe that the TOPS registry provides a big picture view of outcomes that a single institution or a single surgeon's case series simply just cannot provide.

As we continue to develop the TOPS program, we'll be exploring ways to maximize electronic health records and registries to facilitate data into our interoperability. As a professional society, we're committed to our role of providing our members with the tools and data to improve their performance that result in safer procedures, better clinical outcomes, and patient satisfaction. We believe these efforts can inform and supplement global data collection to enhance the postapproval studies and breast safety. We are also prepared to make these tools available to the FDA and industry to facilitate the needed integrated data collection in conjunction with the postapproval studies. I thank the Panel for your time.

DR. LoCICERO: Thank you.

Our next speaker is Dr. Steven Bonawitz.

DR. BONAWITZ: Members of the Panel, thank you for allowing me to be here today. My name is Steven Bonawitz. I'm a board-certified reconstructive plastic surgeon and Assistant Professor of Surgery at the Johns Hopkins University School of Medicine with an appointment also with the University of Maryland in Baltimore. I also serve on the Government Affairs and Health Policy committees of the American Society of Plastic Surgeons. In my practice, I use both saline and silicone breast implants to treat patients seeking breast reconstruction after mastectomy and for the purpose of cosmetic breast augmentation.

I have no conflicts to disclose to the Panel, and my travel today

is paid for by the American Society of Plastic Surgeons.

The focus of my testimony today will be to share my clinical experience in treating breast cancer patients who seek reconstructive surgery. I have been treating breast cancer patients since 1994, and my approach to reconstruction includes the use of techniques which use the patient's own tissues such as the TRAM and DIEP flaps, as well as the use of saline and silicone implants.

Reconstruction involves very important and very personal decisions on the part of my patients and a very careful exploration of the options available to them. My patients struggle not only with an unwelcome diagnosis, but also with the invasiveness and loss of control which accompanies the treatment of any serious illness. Women with breast cancer seek reconstruction in order to restore a sense of normalcy and well-being to their lives. Many of them are not candidates for procedures which use their body's own tissues or do not wish to subject themselves to longer and more complicated operations and the additional scarring that attends them. This is especially true with younger women today. We know from our work with these patients that it is important for them to have options for their reconstructive care and access to different devices that will suit their particular reconstructive needs.

My primary objective is my patient's safety and returning a sense of normalcy to their lives. Breast cancer patients are often

overwhelmed, vulnerable, and scared. For myriad reasons, many breast cancer patients prefer implants for their reconstruction. They want to know that they can regain that sense of control over their bodies and feel like themselves again. Women who choose breast implants often report a desire to feel whole again after the loss of a feminine organ. Often, these women feel that people are viewing them as injured or different and, in fact, often they view themselves that way as well, and an implant may be critical to returning that sense of normalcy. Many times, they have been through a long and grueling course of treatment, and that is finally coming to an end. They look forward, at that point, to returning, at last, to their normal lives. Restoring their self-image through reconstruction is critical to completing their treatment and to moving on.

Over the course of my 17-year career, breast implants have remained an important and popular reconstructive option for my patients. Recent publications in the literature have demonstrated that implant reconstruction is the preferred choice of reconstruction in many young women undergoing reconstruction, and many of these women are also now choosing bilateral reconstruction.

Further, in a recent survey of female plastic surgeons, it was reported that two-thirds of them would choose silicone over saline implants if they were to require breast reconstruction. This is indicative of the confidence that women continue to express in these devices.

As stated by my colleagues, the American Society of Plastic Surgeons remains committed to data collection and to the postapproval studies. It is important for my patients to have access to the most advanced and innovative products that are improved over time. There are new devices in the FDA approval pipeline that will be impacted by changes in the postapproval studies. It is important that science prevails over anecdote and that innovation continues so that the best possible options are available to patients.

I hope that this Panel will support patient choice by recommending improved postapproval studies that facilitate dialogue in terms of bringing new and improved products to the market. I ask that you consider the impact on reconstructive patients as you continue your deliberations, find workable solutions and alternative data sources that provide needed scientific information without stifling access or innovation. I thank the Panel for your time.

DR. LoCICERO: Thank you.

Our next speaker is Dr. Andrea Puscic.

DR. PUSCIC: Good morning. Thank you for this opportunity. My name is Andrea Puscic, and I am a reconstructive plastic surgeon at Memorial Sloan-Kettering Cancer Center in New York City. I use both silicone and saline breast implants when I perform breast reconstruction surgery. I completed a Master's in Epidemiology at Johns Hopkins in 1997, and the

focus of my research since that time has been on measuring patient-reported outcomes in plastic surgery. I am the current Chair of the Clinical Trials Network of the American Society of Plastic Surgeons, and I am pleased that I will now serve as principal investigator along with Cara Krulewitch in the development of a new breast implant ALCL registry.

In terms of transparency, let me state that I am a co-developer of the Breast-Q, which is a patient reported outcome questionnaire which is owned by Memorial Sloan-Kettering Cancer Center and that I receive a share of licensing revenues based on their inventor sharing policy. I have no financial ties to companies that manufacture breast implants. My travel was paid here by the ASPS today, and our mission statement has been provided.

Today, I would like to briefly address the Panel regarding our support for improvements to the postapproval studies, as well as a potential collection of supplemental data to support these studies. Let me be clear. The ASPS is strongly committed to the postapproval studies, and we recommend that all our member surgeons participate. However, we do believe that additional data outside the existing construct may be useful to supplement these studies. In addition to data being currently collected, new initiatives could be employed, such as data mining from existing international registries to answer questions in the study protocol.

Before discussing our ideas for study improvement, let me first address why changes are needed in the way we're collecting data on silicone

implants. As stated, the ASPS remains committed to data collection on the postapproval studies, but we also recognize the importance of innovation and the future. We should pursue studies that allow breast reconstruction augmentation patients access to innovative products that are being improved over time.

For many surgeons and certainly for the companies, the current regulatory environment simply does not facilitate innovation given the intensive time and resource commitment required. Certainly, there are important elements that should be retained in the large, longitudinal studies, but I would urge this Panel to be mindful of the ways that these large, longitudinal studies may impede the innovation that is essential to developing better products for our patients. What we would like to see, moving forward, is an acknowledgment of the limitation inherent in the current studies and a supplemental approach that will collect further data to ensure safety and efficacy.

To address the need for more complete data, let me begin by acknowledging the Australian, the Canadian, the Danish, the U.K. registries, all of which provide excellent data sources that could be tapped for analysis to supplement the mandated postapproval studies. Supplementary data could create more robust and global datasets; registries such as the TOPS, Tracking Outcomes in Plastic Surgery, database and the newly emerging but narrowly focused ALCL registry could also be valuable adjuncts.

We also feel there may be useful data to be collected from patient reported outcome measures. As I mentioned earlier, I am a co-developer of the Breast-Q, which is a patient reported outcome measure for breast surgery patients. This is an important new tool that allows us to better measure patient satisfaction, quality of life, and adverse events. In developing the Breast-Q, we recognize the importance of a rigorous patient reported outcome measure development, and the FDA guidance in this area was tremendously helpful to us. Through a careful development and validation process, we were able to optimize the validity, reliability, and responsiveness of this outcome measure. With the TOPS registry, we now invite patients to complete the Breast-Q, and we believe these data may also supplement the postapproval studies.

Overall, the postapproval studies are moving in the right direction. We commend the Agency for investigating opportunities to improve the studies and to further inform our knowledge base regarding these devices. The ASPS and PSF support changes the FDA has already made to make it easier for physicians and enrolled patients to complete the study protocol. So, for example, we're pleased to see that Allergan now allows patients to fill out the questionnaire online or by telephone, additionally pleased to see that Mentor had made changes to their study website to make it easier. These key infrastructure changes are important to obtain the necessary postmarket endpoints. The overriding goal must be to make it

easier for patients to comply with appropriate follow-up.

Finally, as Dr. Haeck suggested, we specifically would support a less costly but equally effective alternative to MRI screening for rupture. It has been suggested that 10 years is not an appropriate length of follow-up for these studies, and while it is possible that looking at multiple sources, we could potentially collect better data in an overall shorter time period. We still believe that it is important that these devices be followed up through the 10-year period as many complications and adverse events can occur in the 7- to 10-year range.

I thank the Panel for your time. Plastic surgeons remain committed to continuous quality improvement, the safety of our patients, and we look forward to our ongoing collaboration with the FDA. Thank you.

DR. LoCICERO: Thank you. I would like to open to the Panel, questions for this cohort of speakers. Dr. Whorton.

DR. WHORTON: Question for the last speaker and maybe the earlier speakers. I've been impressed by listening to the society's discussion about their databases, the TOPS. I have one question. To your knowledge, are all the patients that go into the TOPS database, do they include all patients, to your knowledge, that have negative signs and symptoms or anything that indicates an effect whether it's related to the impact or not?

DR. PUSCIC: So the question is what are the characteristics of patients that are included in the TOPS database?

DR. WHORTON: No. In a way. Are all the negative implications, the signs and symptoms of any patient that you see in the follow-up, are those entered into the database?

DR. PUSCIC: So the question is, so then are all patients, are all aspects of outcome captured by the TOPS data and the --

DR. WHORTON: Correct.

DR. PUSCIC: The answer is no. The data collection points that are collected in the TOPS registry are a series of complications, such as infection, return to the operating room, and endpoints that are early -- relatively early postoperative endpoints. We're now working to capture longer-term outcomes and specifically patient-reported outcomes.

DR. WHORTON: Yeah. Well, the answer to my question was yes, you do. How long would you follow, typically, the patients or do you follow them routinely or do you -- it only relates to a call-back or a follow-up by the patient?

DR. PUSCIC: In my own practice or in the TOPS registry?

DR. WHORTON: Your own.

DR. PUSCIC: In my own practice, Memorial Sloan-Kettering, because we're a comprehensive care cancer center, we generally continue our patients -- I see my patients every year. They are invited and encouraged to see me every year, and that goes hand in hand with their cancer care.

DR. WHORTON: What would cause them to not appear a

following year, death or --

DR. PUSCIC: I think also moving to different parts of the world. We have a relatively large group of patients that are also not within the U.S.

DR. WHORTON: Okay. Good. Thank you.

DR. LoCICERO: Yes, Ms. Dubler.

MS. DUBLER: This is Nancy Dubler. I wonder if the prior cohort of speakers could come collectively. I think we've heard some very interesting suggestions for possible use of ancillary settings for the development of the data that we're seeking, and I wonder if it's possible -- I don't know if this is allowed under the rules -- but for people to have a discussion about --

DR. LoCICERO: No, we don't, but you can ask a question.

MS. DUBLER: Okay. I'll ask a question. Is --

DR. LoCICERO: Who else better but a lawyer?

MS. DUBLER: Beg your pardon?

DR. LoCICERO: Who else better but a lawyer to ask a question?

MS. DUBLER: Yes. Right. I'll ask a question. I'll try not to make it leading. And that is, the -- I would like each of you to comment on whether the organizations that you represent and the methodologies that you have discussed would be -- the organizations would be willing and the methodologies might be sufficiently changeable to serve the purposes of data collection that we're focused on at this meeting. Commitment of

organization, I mean financial commitment. You are, in fact, the stakeholders, and do you think there's the possibility for the commitment from your organizations to the gathering of this data?

DR. MURPHY: I would -- Bob Murphy and I gave the little talk on what the TOPS module entailed. And let me just say that the TOPS module was a direct response to recognizing need for national databases and registries. And amongst the house of medicine, perhaps cardiology, the thoracic surgeons, the orthopedics, and ourselves are recognized as the leaders. The TOPS registry has been recognized at the Surgical Quality Alliance, which reports through the AQA which reports through AHRQ as being perhaps the most robust tool that we have in our surgical data registry armamentarium.

As it is now, we can report and just click module outcomes of recognized complications, as Dr. Puscic said, infection, the like, but there also is a textbox for other. That other box could be, as we suggested, be modified in the ALCL, to be sistered up with the ALCL, and we have the capability of then, with the appropriate, you know, connections and linkages, to just broaden that to get the same data points as the Scandinavian registries say. The real key to broadening that is data definition, as you've probably all realized, and so that would be the major linkage. Otherwise, it's just interfacing and deciding where we want to take.

And our society, I'm proud to say, has invested a lot of both

institutional resource and personal resource to have this -- you know, it's a relatively small society when you look at the AMA or others -- be recognized as maybe the gold standard for what, you know, patient-driven outcomes is saying. Dr. Puscic's, you know, pioneering work and being able to link that outcome tool with an electronically-based patient satisfaction module is way ahead of anything that I know.

MS. DUBLER: So what I'm hearing is -- let me be quiet.

DR. YOUNG: We at ASERF are very committed to continuing to get follow-up data on all these patients. Our real problem is financing. It's expensive to conduct these studies, and we have limited finances. If we had unlimited money, we would go at it full tilt.

DR. LoCICERO: And you're Dr. Young?

DR. YOUNG: I'm sorry?

DR. LoCICERO: Your name.

DR. YOUNG: Leroy Young. Sorry.

DR. LoCICERO: Okay. Just for clarification, in terms of TOPS, an analogous database as the Society of Thoracic Surgeons database, which I am very familiar, in order to participate, the institution, usually the hospital, pays a fee to get the software and then provides an individual, the hospital does, to help with data entry. That data is then evaluated. Reports are given back as to deficiencies that the institution is allowed to improve on that. Is that the way TOPS is, and if so, what is your participation rate?

DR. MURPHY: Bob Murphy speaking again. Actually, it's the NSQIP database I think that you're referring to, which is hospital-based, plus the thoracic. There's two of those. So there's two different ways of coming at the problem through the hospital. The TOPS module is different because this is individual physician participation without any hospital or external resource or funding.

This is generated within the American Society of Plastic Surgeons without any external constraints. It's a voluntary participation at this point. We have about 10 percent of membership who regularly participates in this. That said, if we were to make this part of a bigger FDA initiative, that 10 percent, you know, with the appropriate incentives or penalties, could certainly be made more relevant to membership, and we could get -- achieve much higher rates of participation.

DR. LoCICERO: Dr. Whorton.

DR. WHORTON: In your -- not opinion. Do you think your database would be sufficient to investigate long-term sequelae to implant --

DR. MURPHY: I'm sorry. I was talking to Brody. It's Bob Murphy. I would be happy to respond.

DR. WHORTON: We keep hearing about the longer-term implications of local complications. Yeah. We hear people that have only had the implant a few years and, indeed, when we talk about a 10-year follow-up, the maximum time anybody could be in there is 10 years. Most of them are

well short of 10 years. So even -- that's kind of misleading, in a way, to me, for long-term follow-up. It's not really long-term. The bulk of the patients have been there a short period of time. So if we're concerned about long-term complications of implants, does your databases follow patients a long time to get any handle on the long-term consequences of implants?

DR. MURPHY: This database was set up to capture what we recognize as the currently accepted complications, which are not the 10-year outcomes at this point. As we've attested, we are, one, looking in the realm of breast implants, say, of expanding the capture rate, but for all the reasons you've heard in the two days of testimony, you know, it's -- there are multiple players in being able to capture long-term outcomes. You know, certainly, the robustness that TOPS brings to the table is different than other databases, but still, the totality of data capture is not based on the infrastructure. It's based on participation and how we incentivize folks to come back after 10 years or to contact Dr. Puscic from, you know, Lithuania with her 10-year follow-up using a web-based tool, perhaps.

DR. LoCICERO: Dr. Callahan had a question.

DR. CALLAHAN: I had two questions. What year did TOPS start? And then are the 10 percent of people who are of the members who are participating in TOPS, are they primarily associated with academic institutions, or is it pretty 50/50, private practice and academic?

DR. MURPHY: Excellent question. "Crossing the Quality

Chasm" was 2000. TOPS was beta-tested in 2001. It came into its first form, TOPS Version 1.0, in 2002. TOPS Version 2.0 came into effect a few years later, which was, again, an evolving tool based on patient need and doctor's need to know. We have 10 percent. The distribution is very diverse. I couldn't tell you it was 50/50, but it's approximately in that area of private -- a little more weighted to the academic, but it's not overwhelmingly academically populated.

DR. LoCICERO: Ms. Dubler.

MS. DUBLER: I'm Nancy Dubler. What I'm hearing is a conversion of interests and abilities, which strikes me as quite unusual. Here is a society that I really -- and surgeons who I really do believe want to do the best for their patients and are missing some of the data that permits them to do that. There's a basic beginning of an infrastructure of data collection. It's missing an expansion, and it's missing support, but we have some companies who, if something of this sort goes forward, will be bailed out of a quite difficult set of circumstances, which leads me to think they might be willing to put in some money for the development.

So what I hear brewing, with my mediator hat on, is a convergence of interests which might, in fact, permit the FDA to bring together some of the people represented right now at the podium who have access to patients, access to physicians, a standard of care to develop and a standard of care which they want, I'm assuming, to be evidence-based with

companies that have, until now, pretty much bombed out on what their commitment is to develop data, and patient and women's groups who have some focus on the data they would like to see created, and the FDA, which has the overall aegis in this area. I hear a possible working group that may have funding and expertise and commitment and could appeal to its members in a way that might be a quite extraordinary joint effort.

So I want to thank all of you for the perspectives that you've brought and for what I think is a wonderful commitment to the enterprise. So thank you.

DR. LoCICERO: Thank you, everybody. We're going to move on.

Our next speaker is Dennis Deapen.

(Pause.)

DR. DEAPEN: Thank you. My name is Dennis Deapen. I am a Professor of Preventive Medicine at the University of Southern California School of Medicine and Director of the Los Angeles SEER Cancer Registry. I have no conflicts to report.

I want to mention a couple of methodologies that are actually known to most everyone in the room that can be used for long-term follow-up, and the first is the Los Angeles augmentation plastics study. I was caught off guard by being called. I'm sorry. I need to catch my breath. Thank you very much.

This study was the first and the longest study of the safety of breast implants, started back in the 1970s and continues to this day. And it was a cohort study based on a cancer registry, and those kinds of resources are still available today. And in particular, I want to point out that the nation is now covered with cancer registries. Back in the '70s, there were only a handful. The SEER program itself covers 28 percent of the U.S. population. And one opportunity would be for breast implant patients to be monitored through a consortium of the SEER registry members. Another approach is one that's much more recent in its creation, and this is a dedicated long-term follow-up center.

The Children's Oncology Group, also known as COG, is the collaboration of pediatric cancer centers from across the United States. Through the adoption of shared treatment protocols, these centers have raised the survival rate of childhood cancers from 20 percent 30 years ago to 80 percent today, a truly remarkable achievement. Unfortunately, the children's hospitals lose contact with their patients a few years after successful treatment. The National Cancer Institute is highly interested in long-term outcomes, often called late effects of the cancer treatment, well into adulthood.

To serve that purpose, the NCI has created the long-term follow-up center -- I show the website there -- to maintain lifelong contact with these childhood cancer survivors on behalf of all treating centers in the

United States. So this is very long-term follow-up. We're talking children being followed for the rest of their lives.

Initiated last year, this center can update name, address, and contact information over time. The current model is an annual contact with the -- with, actually, their parents until the children reach age 18, collect self-reported health outcomes at whatever frequency is desired. Those self-reported health outcomes can be verified, of course, by collection of medical records, as well as linkages with registries like cancer registries. One particular interest, of course, of the NCI of this cohort is the study of quality-of-life issues that can be collected remotely quite easily and ultimately to provide patient contact information to the pediatric providers that treated these patients in the first place to obtain the long-term monitoring required by their treatment protocol.

There's an analogous situation here where these treatment protocols funded by NCI have late effect assessments, often at 5, 10, maybe even 20 years, but they are rarely performed because the physicians have lost track of those patients. Those patients are now being treated in the adult medical environment. And so this center can bring those patients back together with their providers to meet those late effect assessments and then, ultimately, of course, we can link with NDI to determine long-term survival and cause-specific rates.

Now, that center is currently focusing on childhood cancers,

but the methodologies and the technologies used could be used to serve any patient population to conduct long-term follow-up. Thank you.

DR. LoCICERO: Thank you.

Is Sally Greenberg here? Our next speaker is Sally Greenberg.

MS. GREENBERG: Good morning, members of the Panel. I appreciate the opportunity to be here this morning. I am Sally Greenberg, Executive Director of the National Consumers League. The National Consumers League is an organization that's been in existence since 1899. We were founded to protect the rights of consumers and workers in the United States and abroad. And NCL has, throughout its history, been concerned about the welfare of women and their health.

I am here today because of our commitment to patient safety and our concern that the FDA sometimes relies on postmarket studies to ensure safety and effectiveness of new medical products, but then does not make sure those postmarket studies are completed appropriately. I am not an expert on breast implants, but as a consumer advocate, I know that comprehensive and well-conducted scientific research is essential to ensure the safety of all implanted medical devices. If a researcher loses track of half of the patients, those findings are not useful for determining safety.

The Mentor large study lost track of 79 percent of their patients within just three years. In addition, Allergan lost track of almost half of their augmentation patients after only two years. The adjunct studies

were even worse with one less -- with less than one-quarter of their patients still in the studies after five years. In their core study, Mentor allowed only 58 percent of their augmentation patients for 8 years -- followed -- I'm sorry, followed only 58 percent of their augmentation patients for eight years.

None of those studies met the very reasonable standards that the FDA has set for competent research. I understand that, yesterday, several Panel members asked if the FDA has ever threatened to rescind approval if a company does not complete postmarket study requirements. I think that's a good question because if these companies have a track record of poor research study after study, what incentive do they have to improve their procedures and processes the next time a study is completed?

We want consumers to have safe choices, and that means well designed and well-conducted studies are needed to provide bona fide informed consent for patients. Patients cannot make safe choices on a long-term implanted device if there are no well-conducted studies of long-term risks.

I was also amazed to learn that the patients in the breast implant studies apparently paid full price for their implants and all their medical care. One of the major incentives for keeping patients in studies is to provide free medical exams. They should have provided free MRIs so that the FDA would have good data on breast implant breakage and leakage.

American patients should expect better from those who are

required to conduct studies. The FDA should expect, indeed, should demand better. Thank you very much for this opportunity to speak.

DR. LoCICERO: Thank you.

Is Pamela Bridgewater here?

I want to thank the individuals who submitted transcripts to the registration desk and the link to the video, which will be given to the Panel members so that they can review it before we begin discussion of the next questions.

We have one final individual, Gregory Howard, who was to read a transcript and chose not to read that transcript or submit it to the registration desk, has now requested to speak on his own behalf.

DR. HOWARD: Good morning. Thank you, Mr. Chairman and members of the Panel. My name is Gregory Howard. I live in Woolwich, Maine. I am -- I have -- the only conflict I would have is that my room and board was paid for by the National Research Center for Women and Families. My personal and professional time, I'm not being compensated for.

I guess the first thing I would say is that, first, we appreciate the testimony that Dr. Hammond gave that showed that where there is a will, there is a way. As was pointed out by members of the Panel, there is the ability to get data and to collect it. The issue is whether or not there is a will.

When silicone breast implants were approved in 2006, I would note that they were approved over the advice of the FDA's own scientists,

and I would like to repeat that one more time because the issue was brought up, we shouldn't go unanswered on science. In 2006, the approval was granted over the advice of the FDA's own scientists. The studies that the Panel cited and relied upon were inadequate, and once the FDA approved implants, they removed all incentive for the manufacturers to seriously conduct studies to conform to the follow-up requests for safety data. The data that you've seen is de facto expression of that will.

The FDA has an easy remedy for recalcitrant manufacturers: rescind approval until studies adequately addressing FDA standards are answered. These are the same questions that have been asked for 50 years, 5-0.

As you all know, all manufacturers of breast implants participated in MDL 926, a class-action suit in which medical records by board-certified physicians were evaluated for claimants who showed symptoms of an assortment of covered diseases; ruptures, disfigurement, connective tissue disease, fibromyalgia -- excuse me -- lupus, scleroderma were among the many of the compensated implant-related problems. Over 300,000 women have proven to the satisfaction of the manufacturers that they should be compensated for their illnesses. Billions of dollars have been allocated to cover these injuries.

Ironically, Government agencies like Medicare and Medicaid continue to pay for additional implant patients and, in fact, the U.S. Justice

Department sued implant companies on behalf of the Department of HHS because HHS realized that implant problems were costing them a great deal of money. The companies provided restitution of $20 million from class-action monies for medical care provided by various Government agencies, and at the same time that this lawsuit was being settled, the FDA approved breast implants and put Government health agencies in a position to cover the costs. The drain from public monies for breast implants doesn't make sense.

Now, if we could also take a moment to look at the simplest way at what happens to a patient who wants breast implants, a total cost, including surgeon's fees, use of facility fees, anesthesia, et cetera comes to approximately $15,000 per case. Should a woman have implants at age 22, and that's the age at which the FDA has recommended it's the youngest they should have them, and live until 75, her approximate cost would be 75,000 based on the FDA's own suggestion that implants be replaced every 10 years. The figure does not include the possibility of multiple surgeries for complications during the first five years of obtaining the implants.

If we extrapolate that $75,000 per patient using the arbitrary figure of 250,000 women getting implants each year, the costs are staggering. When our new -- so essentially, what we have is a situation where we're talking about huge cost to American women. I would suggest that the manufacturers be financially responsible for paying for any and all tests, as

was just brought up. In most clinical trials, that's the job of the manufacturer or the person who's trying to get something. And what I would suggest -- it has been brought up about the paperwork that doctors have to fill out. Women have paperwork they have to fill out too when their insurance gets canceled because they participated. It's called, do I pay this electric bill this month or do I do gas, I got too behind on the gas, when are they going to shut it off, because they don't have insurance to cover these things.

The decision to allow these on the market was made by a previous FDA, I would note. Now it's up to you to determine how best to make what we would consider a bad decision right, what I consider a bad decision right. And the question would be then, you have the opportunity to either rescind the application or the approval or to require the manufacturers to pay the costs that women have. And the women's groups that have been here today have expressed an interest in being part of that. And I would note that in the earlier discussion, they were the ones being left out of it.

So I guess, with that, I appreciate very much, Mr. Chairman, your allowing me to speak. I know it was unusual, but it was greatly appreciated. Thank you very much.

DR. LoCICERO: Thank you.

Are there questions for this cohort of speakers? Dr. Deapen, would you mind coming up, please? The databases that you talk about are quite robust and, for the most part, are supported by the NCI, the NIH, and

some local agencies, including the cancer societies. How open do you think they're going to be to collecting more data? Turn on your mic please.

DR. DEAPEN: They are already open to ancillary studies, so it's a slightly different structure than collecting more data. Most of the SEER registries are located in universities with robust epidemiology programs, and so we typically have many additional studies overlaid or -- in addition to the registry. So I think they would be readily motivated to participate.

DR. LoCICERO: Ms. Dubler.

MS. DUBLER: Nancy Dubler. But that would largely -- that would be restricted to patients who are post-cancer receiving implants for reconstruction, she said, with a question.

DR. DEAPEN: No. The first study that I mentioned were augmentation patients followed for the next 30 years to determine if they were going to develop cancer. We actually did not include post-reconstructive patients.

MS. DUBLER: And this is a center that is funded through Federal monies cooperatively through different Federal agencies?

DR. DEAPEN: Well, I mentioned two programs. One is the SEER Program. It's the National Cancer Institute Program, which, of course, is Federal money. In many states, it is now supplanted by CDC money as well through their national program of cancer registries. The last program that I mentioned through the Children's Oncology Group is a collaboration of NCI

funding, but also significant public donations through the organization called CureSearch.

MS. DUBLER: If we are looking for sources of funding to develop a robust database, these could be expanded to cover the issues of concern to this Panel within their present structure of organization. In other words, we're not going to require going back to funders or, Lord help us, to Congress to get authorization for these groups to function in a different way.

DR. DEAPEN: No. We need no new authorization. I've actually spoken to the SEER Program in advance of this meeting in anticipation of possibilities, including creating an aggregate SEER file. The current -- the historic SEER data file that comes from the 17 separate SEER registries has been a de-identified file even though each of us hold fully identified registries in our own location. On occasion, that file is fully identified, and for a project like this would be such an occasion. And the advantage to that is, as I mentioned, you would capture 28 percent of the nation's population in one initiative as opposed to 17 separate states.

If I can take just a minute to give you an example of how the funding works. I live in the grant world, and so what we've done in California is we have a state-wide SEER registry Program, and we created the California Cancer -- sorry -- the California Teacher Study 17 years ago where we enrolled 133,000 teachers in our cohort study, very similar to the Harvard Nurses' Study. And the cancer registry, then, has been the background against which

we have determined the cancer outcomes, but the nice thing about that, being a true cohort study is we can study any disease, and we are in that patient population through direct patient contact, direct linkages with other administrative datasets, et cetera.

MS. DUBLER: One final question. In de-identifying your data to bring together databases, it has been determined by someone that this is not a violation of HIPAA?

DR. DEAPEN: HIPAA excludes state-mandated disease reporting from coverage of HIPAA, so by the time the data arrive at a state-mandated cancer registry, there is no coverage of HIPAA. It makes research -- facilitates research greatly.

MS. DUBLER: Thank you very much.

DR. LoCICERO: Did Dr. Leitch have a question?

DR. LEITCH: Mine was related to this issue. If you don't have the -- you could -- do you have data currently about cancer patients with respect to whether they have a history of breast implants?

DR. DEAPEN: Not in routine cancer registries, if that's what you were asking.

DR. LEITCH: Right. And so to do this, you would -- it would essentially be starting from ground zero of taking patients who -- immediate -- you know, say tomorrow, get a breast implant, then they would be entered in the registry. Is that what you're thinking? Or are you thinking

that say, taking the patients that have already been entered in these studies and then populating the registry with those patients and then working the follow-up of them? What was your thought about that?

DR. DEAPEN: Both of those are feasible. The latter is what we call a linkage study, so you take what you might consider to be a retrospective cohort and you can link that immediately. If you have a roster of implant patients from the last decade, that could be linked with a cancer registry now to determine their cancer incidents over that decade. You have to wait another 10 years to get those results, and our Los Angeles augmentation cohort was a combination of both. We did retrospective, and then we followed them many years into the future as well.

DR. LoCICERO: Dr. Whorton.

DR. WHORTON: What fraction of the 17 are population-based now?

DR. DEAPEN: One hundred percent.

DR. WHORTON: Of the SEERs. Excuse me.

DR. DEAPEN: All of the SEER registries are population-based, as are all state registries.

DR. WHORTON: Population-based meaning, if a cancer occurs anywhere in the state, it's tracked for the rest of its life, no matter where it is?

DR. DEAPEN: Not exactly. Only the SEER registries track for the

rest of their lives. The non-SEER registries are incidence-based registries, so they capture all the incident cases in their state, and they're always population-based. The unique feature of the SEER Program is this, track for the rest of their lives, which is one of the resources that we bring. We're required by the SEER Program to follow all patients for the rest of their lives to meet a 95 percent success rate annually, and we do.

DR. WHORTON: So it would be possible for another database to contain implant cases to be merged with, say a SEER, to take advantage of the background data in the SEER and -- but at that time, it would only include the cancer people in the SEER. It would perform that --

DR. DEAPEN: That's correct. We do those record linkage studies routinely.

DR. LoCICERO: Okay. Thank you. Are there questions for other members -- other speakers during this cohort? Dr. McGrath.

DR. McGRATH: Thank you. Mary McGrath. I have a question for Dr. Young. You were quite definite in your comments that you felt that some type of national registry might be useful, but you were not specific in describing this at all, unlike the other speakers. And I was wondering if we could ask you to kind of explore your thoughts a bit on what you had in mind based on your research background?

DR. YOUNG: Well, to give a little background to this, I was one of the people who founded NBIR, the National Breast Implant Registry, as a

part of the American Society of Plastic Surgery and PSEF. And I also participated in the international registry which was started in a meeting in Istanbul and then in the Australian registries. So one of the things about registries is that you have to make it, for lack of a better word, doable. You have to balance all the things you want with what's really achievable.

And I think, to go back to what Dr. Dubler said, is that my hope out of this is that this meeting would become a springboard for the stakeholders like plastic surgery, the manufacturers and the Agency to work collaboratively to define those things because I think the current PAS studies tried to do too much. The questionnaires were too long. So I think we need to sit down together, and it may mean more than one kind of registry because, to answer certain questions may be one cohort whereas answering questions about other kind of things like local complications is probably another cohort.

So when you ask me to be more specific, I think we would all have to be in a room together and decide what we want and then the structure that would be needed and the incentivization to help accomplish that. Is that a sufficient answer?

DR. McGRATH: It's helpful, but maybe you could tell us, when you helped -- you were involved in the Australian setting up there, breast implant registry; is that what you said?

DR. YOUNG: I was at the meeting when the planning phase of

that to get it started took place.

DR. McGRATH: So what did they want to include in their registry and how was that funded, just so we have more information about how you start a registry.

DR. YOUNG: I don't remember who funded it, but the discussion was exactly what I said is, what can we get without asking too much because either, if the patient fills it out or if the physician's office fills it out, you've got a time commitment. And when we started NBIR, we were mainly interested in local complications and reoperation rates. So that's the data that we asked for. And people were very good about filling that out and complying with it. Surgeons, it was -- the surgeon had to fill it out, and we were getting very good data on that, but the drive-it-off-the-lot thing is it has to be an achievable study, and I think we all need to sit down the room and say okay, what do we really need, what are the questions, what do we need to answer then, and then let's get the registry set up to accomplish that.

DR. LoCICERO: Okay. Thank you.

The Open Public Hearing session of this Panel meeting is now closed. We have a couple of follow-ups. One is, Mentor has the information now concerning when accrual was completed for the postapproval study.

DR. CANADY: John Canady, Medical Director for Mentor. The postapproval study began in February of 2007, ended in July of 2009 with 41,900 patients. The core study began in September of 2000, ended in

November of 2001 with 1,008 total patients.

DR. LoCICERO: Thank you.

Also, the Panel raised a question concerning the platinum issue, and we now have, before the Panel members, a copy of the summary of that, and Mr. Melkerson wants to expand on that.

MR. MELKERSON: Actually, just a couple points of clarification. This is the current FDA backgrounder on platinum issues related to breast implants. And the other issue, this is for the people in the audience, this is something that's on the webpage, so if you want, go to the FDA webpage, type in FDA backgrounder platinum. You'll get the link. So it's the same information that was shared with the Panel. And the last point is, for any product, breast implant or implant in general, we do a full toxicology review prior to even allowing studies to be done on those products.

DR. LoCICERO: Thank you. Dr. Marinac-Dabic.

DR. MARINAC-DABIC: Thank you. Just in response to one of the questions that were raised about, you know, self-esteem and STD [sic] updates that, in fact, had been a part of the FDA's IBIR document and the white paper, we will be presenting that slide, along with the registry details ,after lunch.

DR. LoCICERO: Thank you. So it's now time for a break. I think everybody's probably ready for one.

The Panel members, please do not discuss the meeting topic

during the break amongst yourselves or with any members of the audience. I wish that people would return at 11:05. Thank you.

(Off the record.)

(On the record.)

DR. LoCICERO: Move along here. This is a pretty aggressive schedule, and we want to be sure that we answer all of the questions that the FDA has. And, again, we want to thank everybody, including today's Open Public speakers, yesterday's Open Public speakers for their cooperation and their input. And we also want to thank the two sponsors for being responsive to the Panel's questions. They've prepared the C.F.R.'s for the Panel to be able to see, and they also did their homework in preparing Kaplan-Meier curves for the major complications for each of the -- for the studies that they performed. So we would like to ask each, in succession, to present the Kaplan-Meier curves, and there may be some questions directly concerning those. We would like to begin with Allergan.

DR. GROSS: Thank you. Todd Gross, Ph.D. I'm Senior Director of Biostatistics for Allergan Medical, and I'm also Associate Professor of Statistics with the University of California at Santa Barbara.

And Dr. Connor had asked a question about the Kaplan-Meier curves for our key complications, so I should go over those results now.

This table shows the most frequently occurring individual complications within the core 10-year study, which is a study for which we've

just submitted our final clinical study report. Within the augmentation cohort, you see the key complications of capsular contracture, breast pain, swelling, implant malposition and nipple complications, and then the lower panel is the reconstruction cohort. Again, we see capsular contracture and then asymmetry, wrinkling, and again, swelling and breast pain. This table shows the final 10-year accumulative risk by patient and also by implant.

So I have a series of Kaplan-Meier plots. I do apologize. They're a little bit crude SAS output. As you see at the top of the cohort indication and also the complication indication, so this is the risk over time of developing capsulare contracture indexed on days since implant. And so for each of the Kaplan-Meier plots, I'll just make the following observations. In general, as Dr. Connor had suggested, although the rate does increase over time, there isn't a marked acceleration of the rate of increase, so we see that for capsular contracture. Here, we see -- pardon?

DR. CONNOR: These are all core patients?

MR. GROSS: Correct. Okay. This is breast pain. And I would also like to make the point, for several of these complications, as Dr. Avelar had mentioned, you'll see an initial increase because many of these are postoperative in nature and then a very flat increase over time. Here's implant malposition and finally nipple complications. It's a very similar profile over time.

We've also included plots here for some of the other less

frequent complications that might be considered particularly relevant from a patient perspective. So here's the risk of developing rupture. This is within the MRI cohort only. And you see here a couple of step functions. Those are based on the annual -- based on the timing of the visits where MRIs are expected according to patient labeling.

This is a curve of implant removal where replacement of the implant has been performed and implant removal where there has been no replacement. And then, finally, this is the graph showing reoperations for any reason, included device-related and patient selection.

And then I'll just quickly go through the same slides for the reconstruction cohort. Here's capsular contracture, the postoperative complication related to asymmetry, wrinkling, swelling, and breast pain. And then also, rupture. And here again, what we see in this cohort is perhaps greater increase on the time points where MRIs are required and then implant removal with replacement, without replacement, and reconstruction, reoperation.

Now, this is within the BIFS study, which is our large postapproval study, and here we see complication risk rates for capsular contracture and implant rupture.

DR. CONNOR: Can I make a comment here? So this seems to be very, very concerning to me, that three-year rates are lower than two-year rates, so we know that can't be true. So the three-year estimates, we know

why, are just in a smaller group of people because you're losing people, but this seems to me evidence that we're not losing track or you're not losing track of the people who are living happily ever after, that many of the patients that you're losing track of are patients who are, you know, having bad events, like you seem to be losing track of between your two and three, maybe, of patients who had reoperation or had removal rather than continuing to track them. So I think that's just a comment, but that's something that I glean from this slide.

DR. LoCICERO: And, again, what is the denominator on these, year two and year three?

MR. GROSS: So there are 12,500 subjects that have reported through the two-year questionnaire and 28,000 who have reported their three-year questionnaire. So I appreciate Dr. Connor's observation. I would say that we're very early in the three-year window, so there certainly may be a possibility that women who report early within a window are maybe having good outcomes, but we would want to reserve judgment until we're well through the third year window.

DR. CONNOR: All right. So that may be noise, even though it looks dramatically lower. Okay.

MR. GROSS: Yeah. And then this is just a detail slide showing the reasons for reoperations within core by frequency of occurrence. And this is within the reconstruction cohort. And then, finally, we have the same

sort of breakdown for implant removal and for the reconstruction cohort.

Any questions?

DR. LoCICERO: Okay. Thank you.

Got one question from our two -- our surgeons here.

DR. McGRATH: This is sort of a clinical question. The rupture rates appear to be higher in the reconstruction than in the augmentation patients by everything you've looked at. During the presentations yesterday, it was suggested that about 60 percent of the ruptures appear to be related to handling of the implants. Why do you think it's higher in the reconstruction ones than in the augmentation ones? I mean they're -- both sets are handled.

DR. AVELAR: Rui Avelar, Chief Medical Officer for Allergan. I don't believe we use the 60 percent number. It may have come from somebody from the -- our fellow, the other sponsor here. But really quickly, just to qualify, we know that there is a correlation between breast contractures and rupture, so we see a higher contracture number in reconstruction than in augmentation, so we would expect a higher number.

Perhaps the number that you're referring to is what we saw in the data analysis lab, and that's a slightly different number. When we see implants that come to the data analysis lab, at least in our lab, we see a very high representation of failure and a correlation with some sort of instrumentation that led to its ultimate rupture, but that's in the context of

all ruptured implants that come back. They all get analyzed, not just in this core study.

DR. LoCICERO: Dr. Leitch.

DR. LEITCH: On the Kaplan-Meier curve regarding reoperation and reconstruction patients, I -- if I'm interpreting that correctly, high proportion of the reoperations in very early term, is that correct? Am I interpreting that correctly? Yeah. So --

MR. GROSS: Todd Gross again. Yeah, that's correct.

DR. LEITCH: Yeah. So I think some concern was raised by some of the people that spoke from the public regarding, you know, the high reoperation rate for the reconstruction patients and, you know, a lot of that is related to refinement of the initial result. And so -- and that's commonly in these first two years when that occurs. So thank you.

DR. LoCICERO: Dr. Galandiuk wanted to --

DR. AVELAR: I just want to --

DR. LoCICERO: I'm sorry. Go ahead.

DR. AVELAR: I just want to address the reconstruction. I actually broke out yesterday one of the reasons -- one of the high reasons. I think the number one reason for the reoperation was a contracture. The number two was actually needle biopsy. So a lot of these patients, when they're being imaged, when they're followed, they have reason to have a needle biopsy. So -- and then I think in the top five anyways is a size

exchange. So anything that leads to a scar, revision to a biopsy, would be qualified as a reoperation.

DR. LoCICERO: Dr. Galandiuk.

DR. GALANDIUK: Just a clarification for me. In the core study, I believe the MRIs were paid for. And the right side of the Kaplan-Meier curve for the augmentation in the rupture MRI cohort, how many patients were followed with MRI up to the 10-year period?

MR. GROSS: Hi. Todd Gross. Let me just bring up the graph. So you were talking about?

DR. GALANDIUK: The augmentation patients on the -- that graph on the right side. How many patients were followed out there?

MR. GROSS: How many participants in the MRI --

DR. GALANDIUK: Um-hum.

MR. GROSS: -- cohort in core? We'll have to look that up and get that to you. Thank you.

DR. LoCICERO: Any other questions for Allergan? Okay. While you're looking that up, let's get the presentation ready for Mentor.

DR. CONNOR: And do we have their slides? I had both Allergan's, this and the CFR -- or the CRFs, but I don't have either one for Mentor. Has that been distributed?

DR. LoCICERO: The graphs were submitted in paper form and the CRFs, we still need. The Mentor graphs are the color ones. No. There

were two -- there were three submitted yesterday.

DR. WIXTROM: Okay. So here's the Kaplan-Meier plots for some of the Mentor data. I think you should have printed copies of each of these, which may be a little bit easier to see. I don't know if it's possible to turn on the lights in that corner of the room or not.

So what we see on the first slide here is -- oh, and I'm Roger Wixtrom. What we see on the first slide here is capsular contracture Baker III and IV, and as I mentioned in some of my comments yesterday related to when these complications occur over time, we see that, particularly for the augmentation cohort, actually even for reconstruction, that within the first 12 to 18 months, the majority of contractures shows up in that time period. Certainly, it continues to increase a bit more over time with reconstruction than with augmentation. Actually, from a research perspective, that's actually a useful finding because in terms of some of the ongoing work to try and address capsular contracture, one can get a bit of an answer within the first -- within a 12 to 18-month time frame.

With respect to infection, I think these findings represented on this slide aren't too surprising. Most of the infection you see is in the immediate postoperative period. There's really not much change over time. Then these are the results for reoperation. Again, one sees that the majority of reoperations are in the first 12 to 18 months, although this continues to increase over time for the variety of reasons you heard yesterday.

This slide reflects device removal, explant with or without replacement, and again, you see the course over time, and for augmentation, it's a significantly lower rate and seems to have plateaued much more than for the other groups.

Now, if we're looking rupture, these are the results, the Kaplan-Meier results through six years. There's some ongoing discussions on the methodology and estimates at the eight-year time point. This relates to what I mentioned in yesterday's comments for the primary augmentation cohort. One really doesn't see much of a rise in that curve, really, until about the six-year time point. So those are the key complications results, and again, this is from the core -- these are the results from the core study.

DR. LoCICERO: Questions? What is the denominator at the start?

DR. WIXTROM: The total number of patients in the study were 1,008. I believe it was 552 for the augmentation cohort; 251, I think, for primary reconstruction; less for the other two. And I would also concur with the answer in the previous presentation with respect to the high rate of rupture in reconstruction patients, which has pretty much -- I think, pretty much been a universal finding over the history of breast implantation. That really is -- I think that there's strong concurrence with the thought that it is the higher rate of capsular contracture that's then -- which is a recognized risk factor for rupture.

DR. LoCICERO: Okay. Thank you very much. One question from Ms. Dubler.

MS. DUBLER: The implants that are done for reconstruction, are they generally done concurrent with the breast surgery for cancer?

DR. WIXTROM: They can be -- I might defer to a plastic surgeon to give more detailed answers on that, but there is both -- there are both primary -- I mean there's both immediate and delayed reconstruction.

MS. DUBLER: And --

DR. WIXTROM: So in some instances, it is done at the time. In many cases, it's delayed reconstruction done sometime later.

MS. DUBLER: And do your data pick up that difference?

DR. WIXTROM: It isn't reflected in these graphs you see here, but that is something that is tracked in the data, and that's something that's analyzed. Those data are analyzed separately to look at that. Yes.

MS. DUBLER: Thank you.

DR. LoCICERO: Dr. McGrath.

DR. McGRATH: One other thing about that group of patients with the reconstruction, has there ever been any exclusion in either sponsor studies of patients who had radiation either adjuvantly after they were reconstructed or someone who had had a -- you know, a previous lumpectomy with radiation? Have those patients been included in these, just like other breast reconstruction patients? Because they're really such a

difficult group with such a hostile environment for implants, but are they mixed in?

DR. WIXTROM: Excellent point. Yes, they are included in and, in fact, one of the things that's tracked in both of these studies is if the patients have either radiotherapy or chemotherapy. Radiation therapy in particular is an established risk factor for capsular contracture, and there's quite -- you know, an ever-increasing number of literature publications on various attempts, particularly in terms of timing of reconstruction, timing of radiation to try and address that issue, but yes. And those patients are included in the study.

DR. LoCICERO: Dr. Vega.

DR. VEGA: Also, are patients included in that study that have keloid? As you know, women of color often keloid, and so that it's a real hard site to irradiate it, if they're being irradiated. Secondly, also, radiation if they have scar tissue that forms in a different way than others, for example.

DR. WIXTROM: Right. Those patients are not excluded. In fact, it was -- I'm very glad you asked that question.

DR. VEGA: Thank you.

DR. WIXTROM: One of the interesting hypotheses that's been out there for awhile is whether or not patients who are more susceptible to hypotrophic scarring, to keloid scarring, would they be more likely to experience capsular contracture. And actually, we just ran in the core gel

clinical dataset out through either seven or eight years, and we looked at the capsular contracture incidents in patients who, at any time, experienced hypertrophic scaring versus those that didn't. And actually, a little bit to our surprise --

DR. VEGA: They --

DR. WIXTROM: -- difference in --

DR. VEGA: Exactly.

DR. WIXTROM: -- capsular contracture, so --

DR. VEGA: Yeah. I know that one.

DR. WIXTROM: Okay.

DR. VEGA: Yeah. Thank you.

DR. WIXTROM: That's good.

DR. LoCICERO: Okay. Could we have the follow-up question for Allergan?

(Pause.)

MR. GROSS: Hi. Todd Gross for Allergan. We're going to bring up the MRI participation numbers.

(Pause.)

MR. GROSS: Sorry about that. This table shows the number of subjects within each of the indication cohorts and as of their last MRI participation. And so we see participation rates in the high 70 percent within each of the cohorts. Obviously, the revision recon, very small cohort, but

very high participation there as well. And I can't recall --

DR. LoCICERO: Okay.

MR. GROSS: -- who asked the question, but confirm that that answers it. Thank you.

DR. LoCICERO: Thank you.

Okay. We would like to move on to focus on the FDA questions, and we have a number of complex questions that still remain. We would like to ask the Panel to please refer to the Panel folders for the questions. I think we can get through Question 2 before lunch.

Although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair. Additionally, we request that all persons who are asked to speak identify themselves each time. This helps the transcriptionist and audience identify who is speaking.

Please, Dr. Krulewitch.

DR. KRULEWITCH: Thank you. Just to update you and Dr. Marinac-Dabic, we will have information on the registries and the responses to the question that was asked about connective tissue diseases after lunch. We're preparing some slides for you.

So this question is, in the future postapproval studies for silicone gel-filled breast implants, please discuss the following:

a. Is it necessary to assess long-term effectiveness?

b. And if so, how should it be measured (such as device survival, patient satisfaction, and the like)?

DR. LoCICERO: Okay. Part (a) is really the crux here, and it is, these devices were approved because they were effective, and then there were postapproval studies that were requested specifically for safety. So does anybody on the Panel feel that these are not effective and require further study?

Yeah. Dr. Hennessy.

DR. HENNESSY: So the function here is that they provide structure. I'm trying to figure out what effectiveness means in this context. It's an object that supports the tissue around the objection. Is that what we're talking about in terms of effectiveness, or is it more than that?

DR. LoCICERO: What we want to do is bring up the -- what's on the labeling as the effectiveness of the product.

DR. KRULEWITCH: Can you put up the label perhaps?

DR. LoCICERO: We are going to see what information we can get here. Dr. McGrath, in the meantime.

DR. McGRATH: Well, first of all, Dr. Cassidy [sic], I've been sitting next to you and it's been very pleasant, but to call this pushing around the tissue is a little bit offensive here, frankly, when we're talking about a woman's breast.

But in terms of effectiveness, I think the effectiveness is the

ability of the device to bring -- to create as -- or to produce as close as possible to the look of a female breast, and I think we have information on effectiveness. In my opinion, and I'm just going to throw this out here, I don't think we need to continue long-term studies of effectiveness. I think that the function of the device to do what it has to do to create a breast mound just on the effectiveness side is established.

DR. LoCICERO: Dr. Honein.

DR. HONEIN: Yes. I just had a question on what's meant by long-term effectiveness. So is this sort of a given that we're looking to see if they're effective for 10 years since the statement's been made that they're not lifetime devices, or what is long-term by the FDA's expectations?

DR. LoCICERO: Dr. Marinac-Dabic.

DR. MARINAC-DABIC: Well, as it was stated before, at the time of the approval, we only had the data that they're shorter of duration. So in most postapproval studies, we are looking into both long-term effectiveness and long-term safety so that, in fact, the benefit-to-risk profile of devices, but that we know changes over time can be updated or refined based on the best available data. So this study, as you know, is designed to be of a duration of 10 years. So, you know, the opportunity, if the study is conducted properly, is that we would be able, at the end of that study, to actually have the information for 10 years.

The duration of the studies vary from device. Sometimes we

ask for three years when to follow up, sometimes for five. It would be interesting to hear what the Panel's thoughts are in terms of -- based on your clinical expertise and other expertise that you bring to the table. Would you think it's meaningful length if you decided to recommend the actual look at the long-term effectiveness? Because from the FDA perspective, you know, we know these are not lifelong devices, and we would like to know, you know, what -- how to base the risk-to-benefit profile determination beyond the approval period.

DR. LoCICERO: Mr. Melkerson wants to make a comment.

MR. MELKERSON: You wanted the effectiveness outcomes from the core study. They were based on cup, circumferential chest size measurement, patient satisfaction, quality of life. The quality of life measures were Rosenberg Self-Esteem, Body Esteem, and the Tennessee Self-Concept Scale and the SF-36, and that was for the -- I believe the Allergan PMA.

DR. LoCICERO: Dr. Leitch.

DR. LEITCH: I think the effectiveness with respect to patient satisfaction and what it's supposed to do, as Dr. McGrath said, I think has been shown. What might be interesting of this though, with respect to device survival would be whether, in these postapproval studies which should reflect the additional training that was done for plastic surgeons about techniques for placement to reduce instrument injury, if that, in fact, has resulted in a

lower rupture rate in the postapproval period because it might be that there would be a longer survival of implants if you had fewer of those injuries. So that might be, essentially, new data that could be gathered that would be different from the premarket data.

DR. LoCICERO: Dr. Glassman.

DR. GLASSMAN: Len Glassman. Yeah. I think the issue here is, as has been previously stated, what the definition or the patient's expectation of long-term is. I think clearly, based on what we've heard, based on the data and based on my own clinical experience, most patients are -- most patients feel that this is effective. It gives them the body, maybe not that they had when they were 22 years old, but gives them one that they're happy with.

I think the issue is, what is the reasonable expectation for how long these things last because, for argument's sake, if they only last five years, someone who spent $25 or 30,000 might not think that's a good investment and they would need to know that. And I think that the data has shown that 10 to 15 years, for most patients, is the expected life of these things as an effective, not necessarily an intact implant, but an effective implant, and I think that's reasonable.

DR. LoCICERO: Dr. Galandiuk.

DR. GALANDIUK: I'm a little confused by this issue when you say long-term effectiveness because whenever I implant a device in a patient,

I tell them it will -- it can wear out or break. For example, an artificial anal sphincter or an INFUSE support. And I tell them up front, if this breaks, we'll have to replace it. And I'm not sure what the Division's policy is with medical devices. I don't think patients expect them to be unbreakable or finite, and that long-term is confusing to me.

The second issue on patient satisfaction, I think, is very stupid because there are numerous studies in my field of colorectal surgery assessing effectiveness of operations, and you can take patients who've had the most horrendous postoperative complications and ask them, would you recommend this operation to a friend, and they all answer yes. And so you have to be very, very cautious with patient satisfaction data because I think it can be very, very misleading. But I think this device is effective, but again, how do you measure it? I think you have to measure it by postoperative complications and by rate of device removal for complications of the device, not by contracture, and somehow, I think we have to measure these other rare issues.

DR. LoCICERO: So we're getting information with these postapproval studies and with the core studies that -- in about 10 years -- I'm sorry. In about 5 years is a 10 percent rupture rate, although reoperations may occur, et cetera, et cetera. In my own field where we did a lot valve surgery, when valves were initially out, we just knew that they lasted a few years and we had no further data. And then, over a period of time, we

learned by experience how long those devices lasted. I think the question from the FDA is, does that have to be studied by the FDA and, if so, how just to maybe reframe what's going on. So, Dr. Mount.

DR. MOUNT: I think the burden of proof, as far as effectiveness, has been met, and that was met prior to the postapproval studies. Really, if you think about it, the implant is effective in either enhancing or replacing the breast mound. That effectiveness is not a permanent, just like Tylenol is effective for getting rid of a headache because you don't take one Tylenol and it's effective for the rest of time.

And so I think that the burden of proof really has been shown that it is an effective device in what it was set out to do, and I don't feel that further FDA approval or oversight in the effectiveness is necessary. I think that long-term studies showing how long it's effective is really the burden of the device company.

DR. LoCICERO: Okay. Is that going to be a burden of the device company to continue to study these patients or is it, for example, the burden of the clinicians to report long-term effectiveness?

DR. MOUNT: This is Del Mount again. Good point, that I don't think that FDA oversight is necessary for the long-term efficacy to note that. I think that we've had some great suggestions by associations, by groups, by databases that can actually look at that long-term, but I think the burden of proof for efficacious replacement or enhancement of the breast mound has

been met.

DR. LoCICERO: Dr. Marinac-Dabic wanted to make a comment.

DR. MARINAC-DABIC: I just would like to clarify and remind the Panel that this question does focus on future studies, so we're not talking about this particular study, but any other future studies of the new devices that are coming to the market. And also, maybe to clarify another issue why we had this question about the effectiveness, we feel that it's somewhat different when we're dealing with aesthetic devices, how one looks at the risk-to-benefit profile. And some of the questions that have been made in terms of how you actually assess the effectiveness of a procedure might be somewhat different in clinical circumstances when you actually have a procedure to treat a particular disorder as opposed to this kind of aesthetic cosmetic environment.

DR. LoCICERO: So just to go a little bit further, when these devices were initially studied for the PMA, the initial data was two years, I believe, and the Panel -- it was some shorter period of time.

MR. MELKERSON: Three and four.

DR. LoCICERO: Three and four years, and the Panel asked for further information, so additional information was provided before approval was recommended by the Panel, and that was how many years of data?

DR. MARINAC-DABIC: You're talking about what the original Panel recommended?

DR. LoCICERO: The original Panel recommended not approval until further data was --

DR. MARINAC-DABIC: No. I meant the previous Panel.

DR. LoCICERO: The previous Panel that approved it --

DR. MARINAC-DABIC: Um-hum.

DR. LoCICERO: -- was based on how many years of data?

DR. MARINAC-DABIC: I think it's three or four.

MR. MELKERSON: There were two PMAs going to Panel. One had a recommendation for approval, one had not, and one of the -- the PMA that did not have approval was one of the styles was included and was later removed and then approved. But I believe it's three, four -- and Mentor and Allergan can correct me, but I believe it was three years for Mentor and four years for Allergan.

DR. LoCICERO: So at any rate, the point was, in terms of history. The initial Panel was not happy with the period that was -- of information that was available and requested further information. And that second panel then looked at a longer period, which was about three to four years of data, and based on that, that's how effectiveness was established. So I guess now the question is, if a new device comes along, how long are we going to need to study it? Is it going to need to be three to four years as with that Panel, or are we going to need to go longer?

DR. MARINAC-DABIC: If I may just -- the question still focuses

on the new postapproval study. We are not weighing in how long the device effectiveness should be studied in the premarket setting, but the question is for the new postapproval study.

DR. LoCICERO: So once we have information at least of three to four years for a new device -- just again, to understand this better. So once we have three to four years of data and a new Panel, maybe not any of these members here, recommends approval for a new device and there are postapproval studies requested, how long should those postapproval studies go for effectiveness beyond where we stand now? Dr. Connor.

DR. CONNOR: So I think I'm content with the way this one worked, which is where, if you can keep following, you know, that core group of patients out to 10 years, that a 10-year estimate of efficacy, meaning how many are still in the body and how many have been explanted for various reasons, I think that's reliable to data to put on a label and let patients make informed decisions.

DR. LoCICERO: Let's see what the surgeons have to say at this point. Dr. Leitch.

DR. LEITCH: Well, I think device longevity is of interest to the consumer, so I think, as I said, that one particular element of having longer term follow-up that documents that would be helpful to the person who's trying to decide what to do. So I think that is good information to obtain and hopefully, as I mentioned, it would be better if -- if it really is related to

surgical issues and those have been addressed with education, that it would be better at 10 years.

DR. LoCICERO: Dr. McGrath.

DR. McGRATH: I think it's a little bit hard here because it's -- you go back to the definition of what's efficacy and what's safety, which is the core mantra of the FDA. Efficacy, as it was defined back when these studies were set up, these studies, was basically whether the device functioned to produce an acceptable reproduction of a breast. That was the question about the cup size and so forth. And then, whether or not it served to improve patients -- women's well-being as a result of being present, and that was the patient satisfaction surveys.

And, in fact, now, with the core studies, we will or almost do or maybe will shortly have 10 years worth of data that it fulfills those two things. And my understanding is that the longevity of the device, the rupture rate, the survival kind of goes on the safety side in the discussion because, originally, that wasn't defined as one of the things looking at effectiveness of the device. Now, we could change that and we can make that part of effectiveness of the device, but the studies and the way effectiveness was originally looked at, it was mainly whether the device filled the function physically of what it was supposed to do and whether it met the psychologic and satisfaction needs of the patients.

DR. LoCICERO: Dr. Galandiuk.

DR. GALANDIUK: I agree with Dr. McGrath. I think they're two separate issues with regard to safety and efficacy and here, they almost blur together in a way and it's hard to separate them, but the function of the implant or the effectiveness as an implant, I think, is separate from the issues that Dr. McGrath raised with respect to safety.

DR. LoCICERO: Dr. Mount, anything to add to your previous comment?

DR. MOUNT: No. I would just agree with Dr. McGrath that they are effective at enhancement and replacement of the breast mound.

DR. LoCICERO: Dr. Crouch, you wanted to make a comment?

DR. CROUCH: I guess my concern is that there is clear information provided to the patient. So from choosing an aesthetic procedure, I think it's a lot different, as you mentioned, than someone who is having a surgical procedure for a medical ailment.

And so I would just -- I think it is important to look at the long-term effectiveness, at least 10 years to provide clear, plain English information to patients that, if you choose this and you're paying for this, that this device is only going to -- you know, 80 percent chance that you'll need to replace it in 10 years. I think that information needs to be communicated to the individuals who are changing these procedures. And you know, effectiveness could be the device, survival of the device, whether it's intact, but also other reasons why patients would choose to have a

reoperation. I think that's, to me, what effectiveness is, and the patient having the device in for that period of time.

So I would encourage you to continue. I'm not sure that the current postapproval studies are the mechanism to do that given the dropout rate from patients, but I do think it's really important that that information is collected and that's -- you're able to communicate that to the patients in a very clear way that they truly understand that the -- how long this device is likely to work.

DR. LoCICERO: Dr. Callahan.

DR. CALLAHAN: I just want to say I completely concur with what Dr. Crouch just said.

DR. LoCICERO: Dr. Honein, do you have any additional comments? Dr. Marinac-Dabic.

DR. MARINAC-DABIC: Thank you for these comments. I think the question still remains that can be defined as a sub-question to this one. Is the long-term follow-up of the existing cohort the proper mechanism to access the long-term effectiveness, or you foresee potential, some other methods such as cross-sectional look at the data, especially if we adopt some new types of infrastructure strategies, using registry data and gain the additional knowledge by using that type of methodology?

DR. LoCICERO: We'll start with Ms. Dubler.

MS. DUBLER: Nancy Dubler. So it seems to me that that puts

on the table, your sub-question, the issue of FDA involvement going forward when the going forward might be very different than the product device company's singular action. So I would argue to you that it is important for the FDA to be involved, that there is a coordination of data and a breadth of knowledge and perspective and an independence that the FDA brings to the table.

What isn't clear to me at all is whether these two companies have either the commitment or the skill or the ability to go forward in ways that will produce these data. And I'm very interested in a public/private alliance that may produce very good data through very different means, but I would very much think it's in the interest of the stakeholders around this table and in this room to have the FDA involved in that. The more smart people you get around a table, the better your product. So I would argue that it should be on the agenda, that there are data that would be useful to clinicians and to patients considering this medical intervention and that the FDA should be involved.

DR. LoCICERO: So this brings up an issue of the companies themselves and their capacity to handle a large population study like this. So, Mr. Halpin, can you sort of address that issue in terms of resource allocation for Company X?

MR. HALPIN: Yeah. So first, in terms of looking at this question specifically, if you look at the core studies the companies were asked to do,

they established three-year efficacy of their product. What you don't know after that is how long do these devices last before you have a rupture. So they follow the patients in the core cohort for another 10 years in order to establish what those numbers look like in a number of about 1,000.

In the postmarket setting, each sponsor or Sponsor X, in the current environment, would be asked to then do that again only in 40,000 patients. And I would ask, what are the goals, what are you trying to determine there? I think if you're a sponsor, you may want to monitor efficacy in a postmarket approval study, understand the reliability, durability or length of that efficacy before the product needs to be replaced and understand the safety profile on a larger population.

I think the 40,000 patient, 10-year follow-up study may just be too large to -- or unnecessarily large to achieve those objectives, which I think would be sponsor objectives. And I think they want to know that we would want to know it in terms of the durability of the product. If you want to go after other issues like ALCL or things of that nature, I think that may be beyond the scope of any one entity to do and it may need to be a cooperative effort that involves registries and other activities like that. Did I --

DR. LoCICERO: So we're going to stick with --

MR. HALPIN: -- answer your question?

DR. LoCICERO: Yeah. We'll stick with effectiveness here. Safety may come up later.

MR. HALPIN: Okay.

DR. LoCICERO: So let me ask the end-users, the consumers, patient reps here, if they were, you know, told that they needed to follow up for some indefinite period of time and were asked to report the information to an entity that was other than a company or their doctor, how they would respond to that.

DR. VEGA: Yeah. I would like to go -- Marlena Vega. I would like to go back to something that we sort of hop, skip over a lot, and that is, we talk about the psychological profiles that have been created that involve self-esteem, body image, sometimes level of well-being. Although I'm really very, very skeptical about -- this is from my hat on as a patient advocate and my hat on as psycho-oncologist -- that I think that we really need to assess also levels of depression or expectation.

I've had a patient walk in my office who wanted to look like Dolly Parton. So do I, but the bottom line is, we have certain things to work with, and so there are unrealistic expectations. And I'm being, obviously, exaggerated, but there are things within reason that have to be assessed. This is not a magic. It's a helpful procedure, okay? And I think that we have to think about, for the future, if we have some kind of emotional education -- not intellectual, emotional education where we connect with the patient and they're able to really address the confidentiality, but also be able to unburden and talk about expectations, depression, whatever, then I think you have a

hook for the future when you phone call, which is your -- and how to keep them involved in the viability of the study.

I think if you have a plastic surgeon and you go in there and it's a kind of thing which, next -- which we have not seen here today, by the way, and in my own instance, I have not been involved and people are very caring -- somewhere along the line, ethically, morally, somewhere we have to realize that the women who came here had really important things -- I'm sorry -- to talk about. I can't believe that they confabulated all of this.

On the other hand, I also believe that the people sitting on this side of the room, it seems like the Jackson McCoys, care very much for what they're doing and believe very strongly in helping their clients and patients and really didn't get up in the middle of the night saying, now how can I really get these people to pay a lot of money so they -- there's somewhere a balance. What is it Karl Menninger said, the vital balance? I really believe that exists. And perhaps the interlocutor or the means within the middle is by addressing during your initial intake of speaking to your clients and having some kind of psychological profile that you sort of deal with.

I mean after awhile, as a clinician, you get a pretty idea when someone's coming in with the Dolly Parton routine or whether they're coming in because they have a serious question and would like, really, to change their life because of some really bad issues that have occurred. And also, you have -- I'm sorry -- people who are histrionic who come in and they will

always have something that happens that's the matter. Okay. And then you have the other people who really are very well-intended and keep up. So somewhere, there has to be some kind of a profile, in my opinion, and once you get somebody hooked on that, that this for their well-being, I think that you have a better chance of getting people to come back and to cooperate because it becomes not an intellectual process then, but an emotional one.

DR. LoCICERO: Ms. Mattivi.

MS. MATTIVI: I'm sorry. I almost forgot the question.

DR. LoCICERO: So the question is, you know, that you're told -- you're going to get an implant, you're told you only need to be followed for 20 years. You know, you're going to have to go to -- you're going to be contacted by somebody you don't know, some agency that you don't know to do this follow-up, you're going to be part of some database, what kind of response do you think the consumer would have?

MS. MATTIVI: Personally, I would look forward to contributing to that kind of information in an altruistic way. I think the data for these studies, however, have shown that a lot of people are not motivated by that. I think they're -- I agree that there needs to be -- for that kind of follow-up, there needs to be some kind of connection at a personal level, whether that's coordinator in the physician's office, you know, certainly the backing of the FDA or a larger organization, the messaging. I think a lot of getting patient involvement, consumer involvement is about the messaging at a personal

level.

DR. LoCICERO: So we have two physicians on the Panel who don't necessarily have hands-on experience with the procedure and a device, but certainly have a stake here. So, Dr. Jones, what's your feeling?

DR. JONES: I really would be echoing what the other folks have said, but I think that the line between safety and effectiveness here is really unclear to me. Seems like, the characteristics that we put in the safety category are pretty linked to effectiveness so that if you're having contracture or some of these other things, it seems logical that you would not have the same sense of effectiveness of the device. Now, whether you need to continue it for long-term in these postapproval studies, I'm really not clear. I'm not clear that all these questionnaires and so forth really get at what we're trying to get at. I do think that a really clear expectation, and I can't recall who said this, for the patients of how long the device is going to last is probably the key thing here.

I noticed, and I went on both of the companies' websites yesterday and looked, and there's very clear messaging that, you know, you can buy a warranty for this, that it's not going to last a really long time. And that -- I thought that was interesting because it actually put a little bit more responsibility back on the patient to kind of really understand that this device is not going to last a long time, and I'm probably going to have to have it replaced and I might want to invest in a warranty just like you do for your car.

And so I think, you know, having -- you know, the messaging is probably the key thing and not so much measuring effectiveness with the same tools that we were planning on using.

DR. LoCICERO: So before I ask Dr. Glassman to respond, that's a very good point. And let me just be sure we understand from the two sponsors. The warranty exists on all product, and that warranty is free if the patient is registered, and what does that warranty mean?

MS. SLICTON: Araceli Slicton, Allergan. The warranty program for our breast implants offers free replacement product in the case of an implant rupture or a deflation and offers up some surgical cost assistance for that replacement surgery.

DR. LoCICERO: And is that provided with all product?

MS. SLICTON: It is provided with all products.

DR. LoCICERO: And does it cost?

MS. SLICTON: There is a component for -- there is no initial cost -- there is no cost for that warranty if you -- there is an extra cost for the coverage for the contralateral side. Say if one side you want to replace due to implant rupture, that won't -- the contralateral side is not covered.

DR. LoCICERO: Thank you. And Mentor?

MS. SELLEY: Yes. Yes. Mentor has a similar warranty.

DR. LoCICERO: Let's -- Dr. Glassman, do you want to make a comment? Then we'll come back to the warranty issue.

DR. GLASSMAN: Len Glassman. I see effectiveness and safety as fairly different issues at the current time. I think five, six years ago, a lot of people believed that intracapsular rupture was a dangerous thing. It wasn't just a failure of the device, but it put the patient at a risk for a disease, connective tissue disease. We don't really think that anymore, although we've heard lots of anecdotal testimony that, you know, I hope we get to talk about later.

So I think effectiveness is assuming that the surgical procedure does not have operator error. Is the surgical result that you get at Month 1 the same way it's going to look or still an acceptable way at Year 5 and Year 10? You would hate to see an implant had shriveled up over time and became smaller and deformed. So a certain amount of capsular contraction, I think, might be an effectiveness issue.

A safety issue is, do I get a fungal infection, do I get connective tissue disease, do I get some unspecified disease. I'm sick, I know it, but you can't put a name on it. And I think that the effectiveness, you know, a -- some reasonable expectation of time, and I think that the companies or the FDA or somebody needs to be able to give patients an effectiveness number. You know, the average life of these things is 10 years from a you need to have it changed out, and I think there are lots of ways to get that.

You can get it with a longitudinal study that is done by the manufacturer; you can get it with sampling of a registry. Every time an

implant is put into someone, their name goes in a database. It's part of the deal. And periodically samples will be made from those people. Maybe you have yours, you get the -- you get a call at 10 years, and the lady that had it the week before gets a call at five years, and it's simply, this is your implant company or this is the registry, you know, how're you doing, and to get data. I don't think it needs to go on forever, but for a new device, it needs to go on until we have the sense of that number. Safety is a much longer-term potential issue.

DR. LoCICERO: So -- sorry. I think, to summarize it, everybody feels that we need to go beyond. If there's going to be a postapproval study, it should probably be around 10 years, maybe longer, but certainly 10 years would be reasonable in order to get some idea about device survival. And that if we're measuring effectiveness, at least in part by patient satisfaction and psychological measures, that that's going to need to be part of the follow-up because that's part of your effectiveness measure. Unless you can separate the two, I don't think we're going to be -- we're going to have to measure both, and that the mechanism by which that's done may vary and that the amount -- that the sample size and exactly how it's measured may be something that's going to require discussion with a much -- with the stakeholders that are involved, which probably should include the consumers as well in order to establish something that is going to be reasonable for everybody.

Are there any additional comments to that? Dr. Leitch.

DR. LEITCH: Well, I don't know that we need to do the patient satisfaction thing again. I mean, I think that's done. I mean I think that's, you know, pretty consistent and done, so I don't think you have to do that. I think it is more of this issue of the -- you know, in my mind, really, the longevity is the issue and not really patient satisfaction because that question has been pretty well answered, I think.

DR. LoCICERO: Dr. McGrath.

DR. McGRATH: I would agree with that, absolutely, Marilyn, because there were five different pieces to this cohort study. I mean five different psychological profiles running and that data's in. We know the numbers. They're very solid, but -- and I -- excuse me for -- I can't help it because I'm a teacher, but we have an enormous literature on patient reactions to these operations, and those of us who are involved in this world know that we have looked at patient satisfaction, if you want to call it that, but more than that, the real well-being of patients with these devices and with enormous scrutiny over a period of time; we have robust literature on it. It's very much interaction with patients.

Ms. Vega is very much a part of the training paradigm for young plastic surgeons. We spend enormous amounts of time on this because our people have to be able to communicate and pick up on the cues that you're talking about. So I really think this piece of it is -- and also, it's very

time-consuming administering five or six different psychologic profiles. So I agree with Dr. Leitch that I think this is done, and I don't think that that piece of that part of the effectiveness or the measuring of bra size or looking at, you know, how big people get need to be done again.

DR. LoCICERO: Okay. So we have some disagreement about that, but other than that, Dr. Marinac-Dabic, have we answered Question 2?

DR. MARINAC-DABIC: Yes. Thank you.

DR. LoCICERO: Great. So we are now ready for a lunch break. Panel members, please do not discuss the meeting topic during lunch amongst yourselves or with any member of the audience. We will reconvene in this room in approximately one hour, at 1:00. Please take all personal belongings you want at this time. The room will be secured by the FDA staff during the lunch break. You will not be allowed back into the room until we reconvene. Thank you.

(Whereupon, at 12:10 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:08 p.m.)

DR. LoCICERO: We would like to reconvene the General and Plastic Surgical Devices Panel on silicone gel-filled breast implants for the last afternoon. Before we get back into the questions here, we would ask the FDA to provide us a little more information, and Dr. Krulewitch now is ready to do that.

DR. KRULEWITCH: Thank you. First of all, just an update on the question of -- I presented numbers earlier related to all breast implants for augmentation and we reported in our white paper, which we have as our numbers, that it's half and half for silicone and saline, just so that that 296, you can get a sense of how many of those were silicone gel.

What we have on the screen right now, I have two slides. There was a request to get a sense of what kind of registries are out there and what information is in them. This does not include the TOPS registry that was discussed earlier, but it does have a little information on the second slide about the LA registry that was referred to -- that was also discussed earlier.

So these are just a number of different registries. I'm not going to go box by box on this, but you can see that the three here, in particular, this is a Canadian and then there are some Scandinavian ones here. Numbers range anywhere from as high, in the Canadian cohort, of 24,000 plus to lower numbers of 1,000. Some of these are a little bit older, such as this Danish

cohort, which is 1977 to 1992. Many of them are collecting both preoperative, which is this column here, and postoperative elements. Some of them, we don't have information on all of those. Some are a little longer. This is a seven-year registry. Some are linked to other types of data, such as the Danish and the Finish Registry.

And on the second page, there are more. There was the International Breast Implant Registry was also referred to here, which that one goes up to seven years. The specific complications we do not have complete information on, and I think it would take a whole talk and a long time to go over all of those. But you can -- I hope this is giving you a sense. If you have further questions, please know that this full table is in your Panel packet, and most of this information is there. This is the registry that was referred to earlier from LA.

So I'm going to move on to one other response that we had if you -- and we can take questions on this after I go through all of this. There was also questions about connective tissue diseases. As reported in the white paper, there was a concern of the rates seeming to be lower than they were in earlier data. Some of this data was presented by our sponsors earlier, and you can see there were 28 confirmed cases in the 8-year follow-up of Mentor and 9 diagnoses of CTD in the Allergan study. This is also in the Panel pack and this is also in the white paper.

And just to give you a sense of it, as far as numbers from what

was reported at 4 years and 10 years, you can see that the numbers are -- there is an increase, not significantly, but the numbers are higher at the 10-year than the 4-year because they're cumulative. Pardon me. And this is for the Mentor study and the same pattern.

And then looking at self-esteem because there was a concern about satisfaction at 10 years and there was a view both -- an evaluation both by Mentor and Allergan. This is the Allergan data where, across the board, there were no differences in self-esteem from the 4 years to the 10 years. And with Mentor, there was -- pardon me -- a little bit of an increase in satisfaction or positive attitude scores from approval to 10 years. And that's all I have for that.

DR. LoCICERO: Does anybody have any questions. Yes?

MS. MATTIVI: Kris Mattivi, the Consumer Rep. I was just wondering, with the connective tissue disease slides, those are confirmed diagnoses or those are complaints of signs and symptoms?

DR. KRULEWITCH: Those are confirmed.

DR. TOPALOGLU: Confirmed. Not -- yeah. It's confirmed diagnosis.

DR. LoCICERO: Was Allergan -- you need to repeat that. We didn't understand it.

DR. KRULEWITCH: It's confirmed diagnoses.

DR. LoCICERO: Dr. Connor.

DR. CONNOR: So there's been a lot of discussion about how we might use registries, but it's hard for me to see here, at least to the extent I can see, it doesn't seem like any or most of these registries are continuing to enroll patients. So can you speak to if any of these are actually actively enrolling new women who are receiving implants? Because I'm seeing dates like, ending in '89 or 2007 or 1999.

MS. BONHOMME: Right. These are -- the information in these tables are based on published papers from the registries, and I know that the Danish registry is continuing to collect data. The International -- it's the IBIR, was one that looked very promising to us in terms of the level of detail that that registry collects on implant information, but that registry has not been collecting data for some time.

DR. LoCICERO: Mr. Melkerson.

MR. MELKERSON: Just for the transcriptionist, that was Michele Bonhomme that was speaking, and please make sure you're identifying yourself first.

DR. LoCICERO: Yes. Dr. Honein.

DR. HONEIN: Peggy Honein. In the registries, can you give us any sense of the devices we're talking about today? Were they approved earlier in Europe, so some of these earlier dates would actually provide data from the registry on devices that we're looking at that were approved in 2006 here? Because I agree with Dr. Connor. Most of this seems pretty seems

historical, but I know timing of approval can vary.

UNIDENTIFIED SPEAKER: I could get back to you with more specific information about which devices are covered, but I think, for the most part, they are the older models of implants.

DR. LoCICERO: We have a -- somebody from Mentor who's burning to speak about this.

DR. WIXTROM: Yes. With respect, specifically, to the Danish registry, that does include the current devices that were being evaluated by both the core and large past trials.

DR. LoCICERO: Thank you. Other questions for the FDA? Dr. Hennessy.

DR. HENNESSY: Yeah. So do -- so a registry enters people when they get the device, but it doesn't necessarily provide follow-up information. Do any of these registries that would have information, would have recipients of the current devices of interest also have the follow-up information that we're interested in, and if so, where would that information come from?

DR. KRULEWITCH: Well, in the last column here, you can see that there's -- that that gives a little information about length of follow-up or how they're linked to other registries. For the Danish registries that were just referred to here, there appears to be -- oops, I'm on the wrong slide. Sorry about that. Either it would be the three to -- three months to one-year follow-up, or it's linked to various hospitalization and cancer and death

registries as well. So -- and this is a little alive today. So the answer, it depends on the registry, but most of them are doing some sort of follow-up, or linking is what it appears to be from what we found in the literature.

DR. LoCICERO: Ms. Dubler.

MS. DUBLER: I have a policy and precedent question for the FDA. In your history of dealing with postapproval studies which are the responsibility of the company producing the product or device, is there any history of your setting up public/private partnership between and among physician groups and organizations and the company and the FDA and databases? Is there anything like that that you've ever done before?

DR. MARINAC-DABIC: Well, that's a very timely question because, if you recall from my presentation yesterday morning, this is the direction where we are going in terms of setting up the Medical Device Epidemiology Network, which is geared towards, you know, advancing the methods, building the infrastructure, including upon stakeholders' input. And as a part of that, the medical device partnership, we do envision that, certainly, the industry is going to be one of the key stakeholders. We don't have the partnership established as we speak, but this is the direction where we are going, meaning that ultimately there is going to be a venue for this type of research to be done under this umbrella.

There are other examples where, as I stated, that we are working closely with the societies and industry to establish the registries that

will be used to satisfying postmarket surveillance. And as -- again, as an example, a recently held Panel meeting where there was a lot of discussion during the Panel meeting on cardiovascular device, talking about these particular opportunities that present themselves to address specific questions and also build a national infrastructure that will remain even after the postmarket commitments are satisfied.

So that's a very viable option, you know, and I would say that we do recognize, at the FDA, that these studies can be best done if all stakeholders work together, again, recognizing that industry certainly will continue to play a key role because this is the mandate under the FDA approval.

MS. DUBLER: If I could just follow up with one comment, I think that's incredibly promising and optimistic. There is a piece of me, I guess it's the all Marxist piece that thinks that the company will be such a prominent beneficiary that it has a moral obligation to come forth with amounts of funds that would make this possible. Having said that, everybody is a beneficiary, and the surgeons and patients who choose will have the knowledge that they really need to make intelligent choices within discussions between patient and provider.

So I find that very, very promising, and the reason I note it now is that it may change the tenor of some of our answers to some of the questions which you've posed to us because my answer on some of those

questions would be quite different if I see the companies as responsible for continuing these studies or if I see a new private/public partnership as responsible. So I just want to say that in advance to the discussion of some of the other question.

DR. MARINAC-DABIC: If I may add to that, there are a couple of other examples where, not necessarily, the public/private partnership is established. However, in a couple of instances in the orthopedic devices arena, we have been able to work with companies to have them collaborate with certain national registries and supplement the ongoing postapproval studies data with the data coming from, for example, Kaiser Permanente Registry in the U.S. and Australian National Orthopedic Registry to supplement the data already collected under the original condition of approval.

So these are -- we are looking forward to actually evaluate how these precedents are working, but we are very hopeful that it's going to be a good learning opportunity for all of us.

DR. LoCICERO: Any further questions? Yes, Dr. McGrath.

DR. McGRATH: In the models you've just described, those are all situations where health insurance will cover the product, and certainly it would make sense that, using something as terrific as the Kaiser database would be a great way to build a registry, but that wouldn't pertain necessarily to a portion of breast implants, to the non-reconstructive ones. I mean,

certainly, the implants that are covered by insurance could be captured in that type of administrative database, but I'm sure you've thought about this. How would you capture the ones that don't have any health insurance base?

DR. MARINAC-DABIC: Well, the beauty of this scenario would be that we essentially tailor specific questions to specific databases and not necessarily capture all the patients, for example, in this particular case, all these four cohorts in the same type of infrastructures. For the ones that are reconstructive patients, that would be one option. And I think, as we talked about, many of these ways how this can work, I think it's really been creative and tried to tailor the approach for the specific question.

For the cosmetic, for the aesthetic, for the augmentation cohort, I think you're absolutely right, the challenges do exist, and I think this is where, you know, the national registry, for example, for these devices would be a good solution to capture the actual patient and procedure. The issue remains, if the revision surgeries are going to be reimbursed for and maybe they are going to be captured in, you know, other types of databases, which can, again, be helpful to address that particular outcome.

There are still lots of questions that we as a group and as a consortium of different stakeholders need to address. You're absolutely right. This is something that still needs some further discussion. And, again, as we move toward figuring out, you know, what are the questions, what are the cohorts, how different methodological approaches can be used to design

those studies, I think we are on the right path.

DR. LoCICERO: Ms. Dubler.

MS. DUBLER: A brief comment. I think that your answers demonstrate why it's so critical for the FDA to be involved as this process goes forward. And my question is, to which I should know the answer and I don't, when the new healthcare law becomes effective and prior conditions are no longer an exception to coverage, will revision of breast surgeries be covered by insurance companies? Does anybody know?

DR. LoCICERO: I don't think we know, but it's a great question to put in the minutes.

MS. DUBLER: I mean that would change the landscape totally in terms of going forward. So someone must know the answer to that, but I don't.

DR. LoCICERO: I'm sure this will be picked up and digested by the insurance companies after our meeting is over.

Okay. And we want to thank the FDA for adding all this additional information. We're ready to go to Question 3.

DR. KRULEWITCH: Okay. So Question 3 is, in the future postapproval studies to evaluate the long-term safety of silicone gel-filled implants, please discuss which long-term safety endpoints should be assessed. And this goes with -- that's it.

DR. LoCICERO: So hopefully we can be succinct here.

Dr. Crouch.

DR. CROUCH: One of the things I would like to see is some characterization of some signs and symptoms that may be suggestive of autoimmune, but not necessarily a diagnosis. My concern is that we have been focusing on an absolute diagnosis of connective tissue disorder, and many of those, I think, are very difficult, and oftentimes patients go through a long, arduous process of being -- getting a formal diagnosis. So if there is a way to collect information about associate signs and symptoms and perhaps past medical history, I think that would be really helpful in future studies.

DR. LoCICERO: So I guess you're assuming that we're going to collect information on connective tissue disorders for long-term? Yes?

DR. CROUCH: Yes, but I would also like -- it's not just a diagnosis, but also perhaps somebody would need to come up with, you know, some sort of list of signs and symptoms that might be appropriate to monitor.

DR. LoCICERO: Okay. Dr. McGrath.

DR. McGRATH: I was just going to suggest that maybe, to help us with this question, if you could put up the two slides. Again, our numbering system, I think, is different from yours, but Slide 50, which has to do with endpoints for safety for local, and then Slide 51, which was your endpoints for safety for rare. And that would give us something to talk about here, I think.

DR. LoCICERO: While that's happening, Dr. Glassman, you wanted to say something?

DR. GLASSMAN: Well, I completely agree about the list of symptoms rather than just diagnoses. We heard a lot of anecdotal evidence, and I would just like to make sure that it really is anecdotal going forward. The other two things would be, even though there is no evidence of cancer, it's an easy question to ask. And the third would be, since we've heard about some fungal infections, that an infection distant from the original surgery.

DR. LoCICERO: You mean distant from the original surgical site?

DR. GLASSMAN: No. From the time of surgery. I'm sorry.

DR. LoCICERO: So temporally --

DR. GLASSMAN: So something temporally distant.

DR. LoCICERO: Okay. Dr. Connor.

DR. CONNOR: Yeah. So I agree completely with Dr. Crouch. And see, I still haven't received Mentor's questionnaire, but I have Allergan's, and it seems like they ask these questions. They ask about hair loss. They ask about, actually, just oral yeast infections, maybe not other types of yeast infections. But they have a nice symptom list, so I think that they're trying to capture this. There's complaints that it's on page 17, and maybe people are weary by that time, but at least that group is capturing it, and I would hope that FDA would request other groups to continue to do the same in the

future.

DR. LoCICERO: So the Mentor thing is on your table. It should be by your place.

Yes. Dr. Crouch.

DR. CROUCH: Barbara Crouch. Just to make a comment to that, one of the questions on pages on the Allergan talks about specific diagnosis. So my concern is that when this gets reported, that if they don't have one of those specific diagnoses, that's listed in their pretty complicated diagnosis, then if they're collecting signs and symptoms, that may not -- they're not -- it's not going to fall under the connective tissue, and I'm not sure how that is being collected and evaluated moving forward. So that's my only concern.

DR. LoCICERO: So go back to the previous slide on local. So do we need to continue to collect information on all of these issues in a long-term study? If not, are there any that we should -- are there some, not all? Dr. Galandiuk.

DR. GALANDIUK: From my point of view, safety would impact basically four issues. The main one would be need for re-intervention, meaning having another operation for the patient, and that could be for a number of reasons. It could be for infection, for pain due to capsular contraction, but the need for re-intervention would be what I would aim for. For pain not requiring re-intervention, I wouldn't assess that. And it could be

for autoimmune-induced problems, which would include both the lymphoma as well as the connective tissue disorders and device failure, but I think re-intervention would be a safety thing.

DR. LoCICERO: And now back to the rare. And I would like to add one other thing here. In terms of ICD-9 coding, there is a code under toxic effects of other substances chiefly non-medical as a source, 989.83, toxic effective silicone. I wanted some discussion about that. Dr. Hennessy.

DR. HENNESSY: Sean Hennessy. So for any study of a large number of healthy women, it's going to be key to reduce respondent burden, and I'm not sure how to both increase the number of things we ask about and reduce respondent burden at the same time. One general solution would be for people who have nothing to report, to have that be a very quick questionnaire, and if they do have something to report, then additional follow-up would be made.

In terms of the ICD-9 code that you point out, if the mechanism of follow-up is going to be through insurance or other claims data, then that seems like it's a possibility, but obviously, people aren't going to know about ICD-9 codes. So asking about them I don't think would be terribly helpful.

DR. LoCICERO: Okay. We can get into the impediments to accrual a little bit later in Question 4, but are there other comments? Dr. Honein?

DR. HONEIN: Peggy Honein. So just to comment about the

reproductive issues, it seemed to be fairly briefly addressed in the summary, both the Executive Summary and the June publication. So what I read seemed to suggest there's not a lot of data to suggest there's reproductive problems, but I guess what I'm less sure of, is there a lot of data to suggest safety and reproduction and how closely have fetal effects been looked at.

And it seems like the birth defects that are being collected in the Allergan questionnaire, while they can report anything, there's a couple of examples there that seem like maybe not your most typical choices for what you would have written down, but perhaps the prior studies have informed that in some way. But I guess I would argue for continuing to monitor the reproductive outcomes, particularly as younger and younger women may receive these implants.

DR. LoCICERO: So we're sort of re-listing the endpoints, both local and rare. Other additional ones that you would add to this list? Yes?

MS. MATTIVI: Kris Mattivi. I'm wondering, and partly from my inexperience with this Panel, but I would guess it's been discussed before, and I would ask the pharmacists whether there are objective blood markers, chemistry levels that could be followed as endpoints.

DR. CROUCH: Barbara Crouch. I'm not aware of any good objective biomarkers of that, but I think it's an important issue to follow these signs and symptoms over time because, as I mentioned yesterday, I would be concerned about there being perhaps a genetic predisposition,

perhaps an environmental interaction and a genetic predisposition. And that's just an area that's starting to be studied in the environmental setting. And we know, from looking on the drug side, that once a drug comes to the market, we find that there's a rare side effect, and there's a certain population that's predisposed to it.

So somehow being able to identify perhaps a subset of patients that are at risk, I think, would be important moving forward, but I'm not sure there's any blood tests that has been validated that would get us to that point, and nor would anybody likely come up with a diagnosis that the diagnosis code would be helpful also.

DR. LoCICERO: So one conundrum that we have, as my mentor used to say, this is like a fishing expedition. We're casting a huge net for data and then expecting to glean something out of all the noise. How can we focus that? Mr. Halpin.

MR. HALPIN: Typically, from an industry perspective, when you're looking at postapproval studies, you would use the core study or the base study for approval and try to identify questions that still need to be answered. So typically, you might have a larger postapproval study, but in a more focused topic area, because your core study didn't have enough patients to evaluate something, but it appeared to be significant. What seems to be happening here is the opposite, that we're sort of expanding the box to include everything in the postapproval study.

So if you look at the core data for this or for future studies, is there a way that we can focus postapproval studies on questions that may not have been answered by the core study. That's typically, you know, an industry expectation anyway.

DR. LoCICERO: Thank you. I think that's a good refocus here that, we're thinking about future studies, not necessarily this one, and at future studies that come for PMA may actually include some of this information and may answer some of these questions, at least to the satisfaction of the Panel. So we're not suggesting then that all this be done, but at least it's on the table to discuss in terms of a new PMA.

So for this particular question, Dr. Marinac-Dabic, is there additional information or have we answered this question sufficiently?

DR. MARINAC-DABIC: I think you addressed all the questions.

DR. LoCICERO: We'll have plenty of time to get more.

DR. CONNOR: Okay.

DR. LoCICERO: Question 4. I think this is where a lot of it will come.

DR. KRULEWITCH: Thank you.

When considering the design of future postapproval studies to evaluate the long-term postmarket safety and effectiveness of silicone gel-filled breast implants, please discuss, and we have -- this is bullet number one. We'll go to the other ones after you talk about this a little bit.

a. The strengths and weaknesses of different study designs (such as all the ones we talked about, new prospective cohorts, registry, administrative databases, et cetera). And in your discussion, please consider the following:

1. The safety endpoints;
2. Optimal data sources;
3. The duration of follow-up;
4. Control and comparison groups;
5. Inclusion of specific patient populations;
6. Outcomes that can be assessed by aggregating data across manufacturers and across breast implant types (not necessarily specific to a particular brand or implant);
7. And outcomes that can be assessed for a given manufacturer by aggregating data across breast implant styles.

DR. LoCICERO: So I would like to begin this discussion by asking our colleagues with more statistical information. Then we'll back off to the clinical portion for those clinicians who do a lot of this sort of research, and then we'll ask the other Panel members.

So, Dr. Connor, why don't you begin?

DR. CONNOR: Great. I think there is great value in registries

and things that academics can bring here. My old advisor in grad school told me once that statisticians stopped smoking before doctors did because that's, you know, one of the first groups to figure this out. So I think that's true here especially.

And I'm going to plagiarize Dr. Glassman, and he said, you know, there's smoke here, but we don't know if there's fire. And some of that smoke might be coming from, you know, autoimmune diseases. So especially with -- regarding number five, it seems like patients who have family history should have, you know, maybe, you know, a better conversation with their doctor, which is a clinical thing. But those patient populations in particular, if a patient with a history of autoimmune disorders or family history, I really want to track those patients. So that's a prospective group I would like to see tracked because that's sort of where the smoke is coming from and we need to see if there's fire there.

I think some of things broader things, it is very inefficient to enroll 40,000 patients to get 400 of them that will have a connective tissue disease or a disease with a prevalence of 1 percent. So having registries, I think, is a more efficient way to do that, but then it has to be highly publicized. I mean we had so many patients who spent their time and money to come here and tell us about their issues but who didn't do something that's seemingly much simpler, which is to go to MedWatch. Many of them did and tried, but many of them seemed not to because they didn't think they

would be listened to or they didn't feel, even if they had, that was a positive experience.

So I think registries are important, that statistically we can do things that are very valuable there, but we need to make sure that patients who are having things that they feel might be related to their implants and, more importantly, patients who are having outcomes who they don't necessarily would think, but we need to know that so we can look, need to know where to go. So that needs to be publicized and needs to be easily available for when a patient has something happen 10 years down the line.

DR. LoCICERO: Dr. Whorton. Mic, please.

DR. WHORTON: I don't know if it's one, two, three or exactly four, but a lot of the studies, depending on whether they're going to be rare or not rare, which you've already discussed, if they're not perceived to be rare, then it would also take 40,000 people in a registry to find that. So a lot of the case controlled type things or the cohort, those are perfectly good with smaller sample sizes to get those issues of efficacy and some of the basic safety out of the way. And then, kind of set those aside, not to not measure them, but when you get to the longer and larger studies, they can be included and the data can essentially be analyzed in subsets. You can wait until later on to pick out the rare events if you can find them.

Follow-up, I think, is very important. And I was going to comment earlier. The issue of like 40,000 subjects was derived for like, a

very, very small precision so that people have this sort of proportion of an event. Once you subdivide that into many pieces, the sample size begins to degrade.

So the point is, I think there's going to have to be a lot of thought that goes into all of these postmarketing trials to say which outcomes are we going to look at for efficacy and safety, as you talked about, what designs would be most efficient and reasonably unbiased for those. And the longer ones are going to be more problematic, and there's where I agree with Connor that the registries are probably going to be very useful to think about building pretty much immediately, if we could. And those can be handled with a nice regression type analysis because you can control certain things and compare them with -- it was a comment, I think -- that can be compared with what may be already in the literature in terms of certain kinds of cancers and certain kinds of effects.

DR. LoCICERO: Dr. Hennessy.

DR. HENNESSY: So in terms of the questions that need to be focused on, I think that the issue of connective tissue disorder is one. The issue of long-term failure rates is another. I think outcomes in people -- in women with devices that have ruptured is a particular subgroup that should be looked at. I think that looking at trying to do one study where we do all of that isn't likely to be successful. And registries, again, are useful for getting a group of people to be followed, but at least in the United States, where

there's not comprehensive healthcare, that follow-up is going to have to involve ad hoc data collection.

DR. LoCICERO: So is -- are you sort of dividing these to some of these -- the rarer ones are going to require longer follow-up or larger studies. The more common ones, local effects, et cetera, may be very small cohort studies. Would you agree to that?

DR. HENNESSY: Yes.

DR. LoCICERO: And Dr. Connor as well. So, Dr. Whorton, Dr. Connor, Dr. Hennessy all feel that the more common can be cohort studies, and the more diffuse nebulous rare require a larger net.

DR. HENNESSY: Yeah. I mean, so it would be nice if we could do -- and case control studies have been done of particular connective tissue disorders, but the issue has been raised over and over again, that a lot of people with signs and symptoms don't get diagnosed with a particular connective tissue disorder, so diagnosis-specific case control studies may not be fruitful.

DR. LoCICERO: Dr. Honein.

DR. HONEIN: Yeah. I just wanted to speak to number six and seven. I guess I think, aggregating across manufacturers and across implants can be very valuable, so taking a standardized approach, I think, will make it possible to look at some of these rare outcomes. I agree with what the others have said. I think it will probably take some sort of case control

approach because I'm not sure you can do a big enough cohort study to get some of the rare outcomes that are being looked at.

As far as a registry, I think that's most useful if it's a registry that captures most or all of the implanted women. So if it's based on the warranty registration or something that would have a high compliance of people registering or that people had to opt out to not be part of that registry so that you had most of the population there, and then when there were study opportunities, you could reach out to the whole group and have some assessment of whether or not you got a random sample to participate in a particular study. But having a way to capture, rather than a voluntary registry that might get you a very skewed population, I think the warranties might be a nice opportunity to reach a more representative group.

DR. LoCICERO: I think the -- that experience is paralleled by the Society of Thoracic Surgeons database. When they first started, there was significant concern by the scientific academic surgeons who felt that it was not going to collect the data because it was voluntary and we wouldn't collect everybody. And as time went on, people saw the usefulness of the database, and they all joined on, and it's essentially one of the better, more robust databases because of the recognition of its importance and significance. So -- but it would probably be the way we would need to go, but we need to impress on everybody that it is important from the very beginning.

DR. HENNESSY: Can I ask a question about that registry that

you're talking about? How is the follow-up data entered and by whom and is -- would that work in this situation?

DR. LoCICERO: It would not because that's a hospital-based system and the -- although voluntary, most surgeons want to be involved in it because it helps to drive how the state databases are set up to look at outcomes, particularly in cardiac surgery. And so you would rather drive how the state evaluates you then to allow the state to impose the way it's going to be evaluating it. So that's a very different setup; don't think it would apply here, again, because it's hospital-based.

DR. MARINAC-DABIC: If I may add, the follow-up for the STS registry is only 30 days, and there have been a number of studies that explore, you know, link-ability of this data with the administering billing data, such as CMS and -- but again, for many reasons, this type of method would not work here. But I do agree. That's a very good example of how voluntary registry evolved to something that captures over 85 percent of cardiothoracic procedures in the United States.

DR. LoCICERO: So taking a different approach, Dr. Leitch, you've done a lot of cancer protocols including some registries. What's your feeling?

DR. LEITCH: So obviously quality of data is a big deal for long-term follow-up. This is probably the biggest issue in registry type, and it does work better if there's some accreditation or approval that is attached to

data entry into the registry.

So what I was going to mention in that regard would be if the TOPS registry was being used and recognized as part of maintenance of certification, which, Dr. McGrath, maybe I'll just speak to, where the surgeons have the benefit, if they participate, of, you know, completing what's necessary for maintenance of certification. That might be an incentive that would be reasonable for the surgeons to participate. You still got to get the patients to show up too, but you know, that would be a start at using that registry as a way of continuing the follow-up.

I mean the -- any kind of registry, whether you have this warranty registry, which is, you know, a good thought and if your manufacturers -- if it was required that hospitals send all devices that are removed back to where they came from, there would -- you know, those are some ways you can try to facilitate tracking.

But in all of this, there either has to be sufficient incentive and maintenance of certification might be, for some surgeons, sufficient for funding. You know, support to do the activity. I mean it takes time to track people down. It takes time to have them fill out questionnaires, and this idea of reducing the number of things -- and we kind of heard conflicting messages. You know, we kind of heard, even from the public testimony, you know, some people complaining that the questionnaires are too onerous and yet saying, well, we need to check for all these different things. So, you

know, you can't have it both ways. You have to kind of hone down on what is a reasonable thing to question and accept that, you know, you don't get to have every single data point you would like to have. And this is true in cancer trials.

I mean it's really hard to get people to hone down on what's the absolute thing we need to get to have a reasonable study. That's what needs to happen here. It can't be that there's 100 questions that the patient has to answer or that somebody has to get the patient to answer. I mean there's work on both sides for that.

DR. LoCICERO: So, Dr. Galandiuk, you deal with your department in terms of research and resources, et cetera. Could you maybe speak to that issue?

DR. GALANDIUK: Well, I agree. I think your point is very valid that TOPS would be a wonderful thing to include here as a maintenance of certification issue, but you have to have a buy-in from the patient as well, and I agree, the longer something is, the harder it is to get to fill out. And I mean we're participating in some postmarketing studies, and I mean, it's just a huge amount of work. And the simpler you can keep things, the easier.

I mean I think Dr. Hennessy's point about making it so that a well patient can fill out a form very easily and it's just a couple of clicks or something and then the patient with symptoms would have a more complicated form. And I think the issues here, in terms of the endpoints, you

have to look at -- we've already brought up -- are important to keep symptom-based.

And with everybody, at least my patients, whether or not they have insurance or money, everybody has a smartphone. I wouldn't see how come, if I can check my banking account in a secure fashion using a smartphone, why you couldn't link a smartphone ap to some kind of registry like this where patients could enter -- do a survey, a couple of clicks if they're asymptomatic, they've already entered data directly into a registry. You wouldn't have PIN entry errors where people -- I have my patients fill out forms illegibly. You would have something that would be legible, and then if they had symptoms, they would go -- the page would come on where there would be a dropdown, where they would go further into the form.

I think one of the problems here is that they don't have any kind of patient advocate or somebody to get them interested. I had mentioned for the reconstruction patients, perhaps getting the Susan Komen Foundation involved. For the augmentation patients, I think we need to get somebody to publicize to them to get interested again. And we're sort of giving up on all the patients that are lost to follow-up in both the studies, and I think that's a valuable resource where all these people have already signed consents. And as Dr. Connor said, if they -- if we get contact with them again, we can still use them in analyses. I think we should try to contact a lot of these people because that's a huge amount of potential data that we could

still access and, I think, would still give us a lot of valuable information that we could then use for future studies as some baseline information.

And I was just, while we were sitting here, I did a search on celebrities who have had implants removed, and half the things you can't believe on the internet, so I have no idea if any of this is true. But a list comes up: Jenny McCarthy, Demi Moore, Stevie Nicks, Jane Fonda, Mariel Hemingway, Pamela Anderson, Loni Anderson. Now if the companies could get some of these celebrities to do an FDA-sponsored PSA on Dancing With the Stars or something like that, telling people who have had augmentation that there is MedWatch available, how important this is for insurance issues to determine how long the -- not to scare people or make them worry that there's some, you know, health scare about implants, but that we're really trying to find out how long these devices last to improve patient care and that it's important for them to report information. I think we need to be sort of proactive and get patients interested in reporting data.

DR. LoCICERO: So that's really an excellent point. It's actually to Part B of this question. So before we go into Part B, I just want to be sure that there aren't some other people who would like to add to what we've got on the screen so far. Yes?

MS. MATTIVI: Kris Mattivi. I just wanted to kind of reiterate a point that was made earlier and one that we discussed yesterday. Just in terms of the FDA being the coordinating entity for some of these postmarket

studies that are across companies or, you know, involving the same device type, but for the FDA to be the entity that leads the design in carrying out these studies, I think, would increase the ability to aggregate the data and then to be able to control for manufacturer or device type would be easier at that point if the studies were designed consistently.

DR. WHORTON: I perfectly well agree. In fact, one of the topics is can you integrate studies that are presumably different. If that outcome variable is identified and defined the same way, roughly, then you can integrate the datasets. You can't just put them together, but you can actually analyze them. It's almost like, consider dataset 1 is a stratum 1 and dataset 2 is another stratum and you kind of -- there are ways to do that. But if the endpoints are different, then it's not really possible.

DR. LoCICERO: Dr. Jones or Dr. Glassman, do you have anything to add from the radiological standpoint?

DR. GLASSMAN: No.

DR. LoCICERO: Well, we'll get to (b) in a minute. We'll get to (b) in a minute. All right. And Mr. Halpin.

MR. HALPIN: The only thing I wanted to say on this point is one trial can't answer all questions that we have. I think, if you look at 1 through 5, you're really trying to answer questions that remain unanswered upon PMA approval. If you look at 6 and 7, those maybe fall into more of class effects that would affect all sponsors. So I would support some of the

things I heard here where maybe collaborative or working off the same protocol or in a registry might be valuable.

DR. LoCICERO: Okay. I think the -- Dr. Whorton.

DR. WHORTON: If you did about four of these studies and you had a long-term, inclusive registry, would all these people that are in these trials go into that registry? Because they're going to be a subset of the registry. So in a sense, you can reach in the registry and pull out subsets to analyze. So if you're clever, you can kind of have a lot of those small studies built into the registry, and you can separate them out later and analyze them.

DR. LoCICERO: I think that's an excellent point, and it would be back, again, to the issue of as long as a registry is sufficiently inclusive of all patients, then that would certainly work.

So maybe at this point, Dr. Marinac-Dabic, do we -- have we answered Part (a) of this question?

DR. MARINAC-DABIC: All right. So we didn't have much discussion about the comparison groups, have we?

DR. LoCICERO: No. So we'll talk about comparison groups. Dr. Connor.

DR. CONNOR: So then I'm glad you reminded us of that because I had some notes there even. And I wonder if there is a way to -- you know, you see ads for research studies on buses and such -- you know, get women who would consider this, but it's just not worth the risk. I mean the

risks seem small. Bad things happen. We really don't know if they're affected by the silicone or not, but there are definitely women who may be interested in this who just think it's not worth the risk to them. It would be fascinating to have such women because these are women who, presumably, may have, you know, whatever self-esteem issues or things that have led women to get implants, but they're just not willing to take the leap. So to, you know, enroll such women would be a fascinating study for -- you know, I don't know who would fund that, but it seems like a good and interesting control group.

You know, of course, then I don't know what other implants may, you know, contain silicone, but you know, even in, you know, if there are heart surgeries or different things where there's silicone placed in valves or in catheters and things like that, that that would seem like good control groups too. But I like the idea of having an active, enrolled group of women who would -- who have contemplated this, but for whatever reason, have decided against it.

DR. LoCICERO: Okay. This really brings up an important point, and that is that we're not necessarily insisting on it, but considering another control study after the sponsor has just finished a PMA and now is being asked to perform another control study. So --

DR. MARINAC-DABIC: If I may clarify the question? I think the question was not asked in a spirit of having a randomized control trial. It was -- the context is, if -- let's say if we do have a national registry for all

breast implants, that can conceivably be the registry of all breast implants, of all manufacturers, all types; saline, silicone. You know, and then that registry essentially can be used to pull the -- actually, the comparison groups from it and be essentially the resource for many types of ancillary studies that can be nested in the registry.

I think the question was also asked in a spirit, would then the comparison group be best defined as a cohort of other patients who have breast implants or perhaps the patients who have other cosmetic procedures or if there are any thoughts or advice that you could give the FDA. And then we certainly are going to go in more detail as when we are in a situation to design the new study.

DR. LoCICERO: Mr. Melkerson wanted to make a point.

MR. MELKERSON: Just one point of clarification. None of the studies, to date, have been a randomized, concurrent control for a premarket approval, but that does beg the question, are there other study designs that we should be considering that may address some of these questions premarket versus postmarket. And I'll just throw it out since I saw it on one of the recent ASPS websites. Bring up the issue of fat grafting versus breast implants versus saline.

DR. LoCICERO: Okay. Dr. Whorton first and then --

DR. WHORTON: I was going to make the same point. You compare saline with the silicone. You could do the -- yeah. You could build

subgroups that you don't expect to have the same impacts with the implants. This brings up another issue, and that is predisposing factors. In the database, the registry, that you should be able to compare breast cancer with non-breast cancer, with or without implants just to see if there are differences in any of those side effects or symptoms because the minute you find the side effects or symptoms, the differences, it's got to be because of something.

DR. LoCICERO: Ms. Dubler.

MS. DUBLER: I just wonder from the surgeons whether there are a sufficient number of women who come for an initial discussion and who, because of the risk factors, decide not to get implants, and could they all be registered in -- would they be a source of people for these studies?

DR. LoCICERO: Dr. Leitch.

DR. LEITCH: Well, I'm not a plastic surgeon, so I don't want to answer that entirely, but you know, again, it's this issue, you're taking a person who doesn't have an intervention and asking them to be followed for a long period of time. And so that's the harder -- to me, that's the harder thing to do. You know, the other idea might be taking somebody who does have an intervention, but doesn't involve silicone, such as a reduction mammoplasty. You know, that might be a cohort of people to think about, but again, you know, once they're fixed and they're fine, they're not going to be -- they're not -- you know, to show up and maintain a long-term cohort.

And I guess the other thing would be, what are cohorts that exist already of women that are followed over time. So some of these Nurses' Health Studies and stuff like that might be, you know, "your comparison group" for these rare events. That might be what you would use as the control group rather than trying to match it out of a group of people who have no symptoms and have no reason to be followed, which would be a lot of -- you know, it would have to be a lot of people to be followed for a lot of time and that -- to kind of redo that is a major effort. And so maybe using some of those existing things would make more sense.

DR. LoCICERO: So those existing ones are probably more going to be like a historical control. So that brings up the question of, in this situation that we were going to compare devices, would you consider a historical device as a controlled one. Dr. Galandiuk.

DR. GALANDIUK: Yeah. I wouldn't use historical device as a control, and I honestly don't know how you need a -- what do you need a control for. Because here, if you need a control for your connective tissue disease -- I mean I'm not quite sure what you're controlling for. If it's for connective tissue disease, you want a population sample, and you want U.S. data on that. If it's lymphoma, you want SEER data for that. So I'm just not understanding what the control is being used for. And if you're comparing devices, you're comparing them with each other and the -- I'm -- you just -- your reference will change depending on how you're doing your statistics. So

I'm not quite sure it depends on that. And I guess Dr. Connor would say how you choose which one is your one you're comparing to, but I'm not quite sure I understand the question.

DR. HENNESSY: Well, if you're looking at rates of symptoms associated with connective tissue disorders in young women, I don't know if there are good data on that. And as this mechanism of ascertainment will likely differ from what's been done previously in the literature, you're always better, if feasible, having a control group rather than having an exposed only cohort because then you know how to put the rates into context. Does that make sense?

DR. GALANDIUK: It does, definitely, but I'm just saying, to get a very comparable group, I don't think, is going to be possible in the plastic surgeon's office, getting a non-exposed group. I mean you could have Botox patients, but the likelihood the Botox patient is not going to have an implant -- you know, I'm just finding it hard to have in that plastic surgeon's office a comparable patient, and there aren't going to be that many reduction mammoplasty patients that are going to be of a significant number.

DR. LoCICERO: All right. Dr. Mount.

DR. MOUNT: Just trying to think about designing a study that would work well with this. The ASPS and the ASEPS did a twin study for face-lifting where one twin got -- one twin sister got one type of facelift, the other one a second, and they followed those patients out for 15 and 20 years.

If I remember correctly, I think 20 years was the final. But that would be about the only way that you could really control for all the factors, particularly the genetic factors. If you had one sister that had breast augmentation and enrolled her in the study and then perhaps invited her to invite her sister that might not be augmented to serve as control, but that would be a very, very small number, I think.

DR. LoCICERO: Dr. McGrath.

DR. McGRATH: I think that the question kind of forces you back to databasing because if you're doing -- casting a wide net and you're setting up a registry that hopefully will capture potentially five, six different endpoints that we're potentially interested in, you kind of need to have additional information about the disease process in different cohorts of people. So let's see if you find cancer, you want to see what the incidence of cancer is in some group and can -- but they'll all have different variables.

So I think the only way that's really going to work is not by building a registry with controls, but instead, trying to take advantage of something, and I think there is some limitations to it, but something like TOPS. Because here, with already a million data points in it, if that thing grows robustly, you will be capturing all the plastic surgery patients, and there will be a database that actually, over time, will have people who are having reduction mammoplasties and facelifts and stuff that potentially would be comparison groups.

Now, one of the limitations of TOPS, first of all -- I agree with you, Dr. Leitch. I think it's going to be very big in plastic surgery. I don't think they mentioned when they presented today, but they're -- it is going to be linked to maintenance of certification. So for a plastic surgeon to maintain their board certification, they'll have to participate in this kind of a database so they can turn in patient outcomes to show a biopsy of their practice. So yes, some day this will be something that's pretty universal.

But the problem with it is two things that I see. One, you really are not going to expect people to have 10- or 20-year data built into TOPS on all their patients. So you're not going to have the ability, you know, to look back at 15 years of some potential control group and look at all their health issues because I just don't think that that kind of data will be kept up. I think it will be terrific for the common complications, for the short-term complications and that kind of thing. I think we'll get that beautifully out of a database like this.

One of the things about TOPS that it's important to mention is there's a lot of implants put in this -- put in in the United States that are not put in by board-certified plastic surgeons. So remember here, you're not -- this is not TOPS, even at its best, will not capture every woman who gets an implant. There's a whole lot of other people out there putting in breast implants who are not plastic surgeons at all, and also, there are other surgical groups now that are increasingly putting in implants. So they won't be

involved in something like this.

DR. LoCICERO: So speaking again about databases, databases keep coming up. So, Mr. Halpin, let's say we had, hypothetically, Companies A, B, and C that all have a product that is in various phases of postapproval study. How willing do you think they would be to share their data in a large database that's going to include their competitors?

MR. HALPIN: I would think that would depend on whether that was -- I think that would depend on whether or not there was an agreement before they actually started the studies to actually pool the data. So I think a lot of this gets into, if you're doing a study, what's the intent of the study, and for most of these studies, the intent would be to create a greater understanding of how your product specifically needs to be labeled and what the expectations are for patients and physicians who are using the product.

If it's a class issue, number six and number seven in particular, I think sponsors would be open to doing -- either doing parallel studies so that you're using the same protocol or working with a registry or using reference points or things of that nature. I think if you're answering questions which are specific for your product, it may not make sense to actually pool that data with another study that's answering different questions about their product. An example where this might come up is if people make innovative designs to their products and then have some postapproval questions about the long-term impact of that design change. It may be different than what's

happening with other sponsors that may put you in a unique situation. Did I answer your question?

DR. LoCICERO: Yes. Thanks. So I think, overall, to summarize where we stand with the issue of controls, they're problematic and that it would have to be very specifically defined and that the individual sponsors and surgeons, et cetera, would need to get together to help the FDA decide on appropriate controls. Does that now answer your question concerning Part (a)?

DR. MARINAC-DABIC: Yes. Thank you.

DR. KRULEWITCH: So for Question 4(b):

When considering both current and future postapproval study designs for silicone gel-filled breast implants, please discuss methodologies and strategies that will increase compliance with:

- enrollment;

- follow-up clinic visits;

- annual questionnaires; and

- MRI screening.

DR. LoCICERO: Who wants to jump in?

DR. GLASSMAN: I'll jump.

DR. LoCICERO: Okay. Dr. Glassman.

DR. GLASSMAN: I've been waiting to jump. Okay. The theory

of second best, it applies when there is a constraint on one or more of the underlying conditions for optimization so that condition cannot be met, then the second best solution is the best. That's for all you statistical people, but it's real.

This was the Mentor brochure. I don't have the other one, but I have this one. It has two major problems. Well, the general problem is, it was an attempt at the best. It's 26 pages long, one problem. Second is, they don't ask for the radiologist's phone number until page 7. That was a joke. Okay.

No. Seriously, I looked at this, scared the living daylights out of me. If I got this as a patient as a paper document to fill out with a pen, I would be out of your office so fast there would be fire coming out of the back of my coat. If I was doing it on the web and I got to about page 5 with no estimation of where the end is, I would hit the escape button and go on and do something else. No wonder we had such low response from patients. And this goes for enrollment. It goes for follow-up visits. It goes for MRIs. It goes for everything. We ask for way, way too much information, and we scared the patients away. We need to be more realistic about what is doable.

I mean there is a question here about alcohol and tobacco use. Who cares? Maybe there's a scientific reason for it, but if I'm a patient filling this out, I think you're all crazy. So you -- we've got to be more realistic about what patients will be willing to be put through, and if we focus on the

questions we really need to answer, I think we'll have a much better chance of being successful.

DR. LoCICERO: Speaking specifically about the smoking, when the first question is, when did you stop smoking and you never smoked, how are you going to answer it? But can any of you speak to the issue of web design, those who have done it maybe? Anybody? Dr. Connor.

DR. CONNOR: So yeah. I think Dr. Galandiuk -- I'm probably not saying that right -- said it best. I mean you -- my company does adaptive designs, and part of that is getting really only the information you need, realizing anything laborious isn't going to get you any information at all. So having web design where you only answered the questions that matter, I think, is the key, and that's simple, and many companies do that. Unfortunately, they're not companies doing clinical research sometimes.

DR. LoCICERO: So yeah, there is marketing -- there are marketing techniques, but there are a variety of companies that do this and a number of organizations use these. I won't mention any names of companies, however, it -- some of them are quite cheap and you can design your questionnaire that has a bar on it that says I'm 25 percent complete, I'm 50 percent complete, you know, how long it's going to take you to get through it, and it can also be layered so that if you answer a question in a certain way, it opens another stack of questions that you have to answer concerning that. So there are a variety of ways of constructing these, and

they're relatively cheap in terms of design because somebody else is already doing it. They do volumes of this thing, and they can make their prices pretty low. So, Dr. --

DR. HONEIN: Yeah. Just to echo the earlier suggestion that was made too, about having this not just on the web, but accessible to iPhones since a lot of people who don't have regular internet access still have access through their iPhone just to make it as simple as possible. I think you have to give people incentives and preferably a choice in incentives. If they prefer to have cash or a gift card or, you know, part of their healthcare visit paid for, something that empowers them a little bit and then having some sort of regular contact via a newsletter that's electronic or paper that gives them updates on the study results also so that they're getting some interim information that what they're doing contributed, there was a value. They can see the loss to follow-up rates and, you know, maybe help the patients feel like they are making a contribution.

DR. LoCICERO: Dr. Hennessy.

DR. HENNESSY: Sean Hennessy. While it would be great to have all the information collectable electronically, I'm not sure that that will meet all the needs. So it may be that, if a certain response is given, that triggers a telephone call back to the patient for a more in-depth discussion, and some of that may need to result in clinical referrals to help them manage problems that they're having.

DR. LoCICERO: Good point. Dr. Galandiuk.

DR. GALANDIUK: But that kind of thing is very easy to build in there, and I mean, it's just so important to design these things well, and I think we've actually worked with a lot of CROs who have done smartphone-based patient reporting, and it really works very well. And if your patient doesn't use it and it's not easy to use, they're just not going to do it, and you might even want to have a little site where the patient can get health tips so -- or a health newsletter or something like that so they feel like they're getting something out of it rather than just being, as you mentioned, some return on investment, so to speak, for their time.

DR. LoCICERO: Dr. Vega.

DR. VEGA: In line with what you're saying is wonderful, especially what you just said. I so applaud you. If we could have on the application or whatever, the question, a number -- remember, we talked about confidentially -- a number that they can be reached at and a time that might be good for them rather than just calling up and you're having somebody sitting with you and your husband there or whomever and you really can't dialogue, it might be very nice to have that. And, therefore, that reinforces the patient's importance as someone who is willing to work with you and empower themselves and their healing.

DR. LoCICERO: So another issue in terms of this is -- we've discussed it a number of times -- is maybe coercion or, you know, the

imbalance. We want to be sure that we have equipoise here in terms of doing this. So, one that has come up earlier is a warranty. We all get warranty cards with our equipment and so on, and we usually pitch them unless you -- unless they say, if you don't turn in a warranty card, your device will not be warranted, and if you turn in a warranty card, we're going to ask you to verify this every few years in order to keep your warranty intact. So, Dr. Dubler, let's address that directly. Now, is that coercion?

MS. DUBLER: My definition of what's coercion is very narrow. That's here's your warranty; you want to keep it, be prepared that we're going to check with you every couple of years. I don't think that's coercive. I mean someone -- you need to give someone the opportunity to say no, but if they understand that it's a way of keeping in touch, if we can make the point of collecting data of interest to people, and I think it will be of interest to women, perhaps even women with augmentation, although people have indicated that they want to disappear, but the altruistic notion that they may help other women.

So I don't think it's inherently coercive, especially if we can say that here it is, it's easy to do, and if we do think you need to come for a checkup, we'll tell you and it will be of no cost to you. Stick with this, and if you need to come for a checkup, we'll suggest it to you, and it will be of no cost. And I think that that package might be appealing.

What I don't want to lose in all of these discussions is -- I hear

us going in a very different direction, which I've said I think is terrific, which is FDA moderated coalition of stakeholders working together to get the best data that we can. But I think there's a quid quo pro for that, which is that the companies who were originally charged with doing these studies ought to have a special obligation to provide the funds that will let us put the sweeteners in the package which will help the new coalition to succeed. So I think all of those pieces, if they come together, that would certainly not be coercive.

DR. LoCICERO: We also had talked about -- Dr. Connor, you wanted to add to that? Okay. We also talked about the issue of using SEER databases. We had the unique information earlier today about that being maybe a way to collect some of this data. What are people's feelings about that? Dr. Glassman.

DR. GLASSMAN: Len Glassman again. I think any way that we can get information without having to do a lot of work is well worth doing. I think it makes it easier. It may be second best information, but there are lots of data sources out there, both national and international and we should -- that should be our first line of searching. What we get out of that, we don't need to repeat. I mean one of the things with the studies that we're talking about here is they were done as if there was no other data but the core study available anywhere. And I think that's inefficient. I think it's expensive, and it obviously made it harder to be successful because we weren't successful in

these two studies in getting the kind of response rate that we needed. So I think it's very important to milk other sources as much as we can.

DR. LoCICERO: Dr. Honein.

DR. HONEIN: Peggy Honein. Yeah. I think the SEER data may be not only less expensive to use, but a superior choice of data for the cancer outcomes because it is collected in a population-based manner. So I don't know that it will get at all the outcomes we're looking at, but for the ones it can, it seems like an efficient, good choice to look towards.

DR. LoCICERO: Dr. Connor.

DR. CONNOR: So I agree that SEER is good for that, but it seems that, to me, other than ALCL, cancer is maybe the least of our worries because hazard ratios are actually frequently way less than one for cancer here. And some of the areas, I think, of open concern are not cancer, and certainly SEER isn't going to want to piggyback with something non-cancer-related, to answer some of the more prominent open questions.

DR. WHORTON: Yeah.

DR. LoCICERO: Dr. Whorton.

DR. WHORTON: I tend to agree. The mechanism as far as the SEER registry may be useful to learn how to set up and run a registry. And it may be useful to look at cancers that may -- you can do case control studies within the registries to see if that outcome is related to implants or not, which you would have to get the implant information -- I think, is probably

less efficient than it's warrantied.

DR. CONNOR: And SEER is so -- I mean it's a huge, laborious thing, but it's so easy in that, if you get cancer, you go see an oncologist. Here, you end up with this host of symptoms, and patients don't know where to go. They see all these different types of specialists. So ending up, you know, with a point of contact that gets you in in one of these administrative databases is so much harder here, and to even figure out who to piggyback on is much harder. I still think we should figure it out, but it's -- I think it's hard to learn from SEER because that was, you know, low-hanging fruit compared to what we're being asked to recommend something on here.

DR. LoCICERO: Dr. Galandiuk.

DR. GALANDIUK: For just a single state, something like California, it might be easier to use than non-de-identified data and somehow try to merge it with some of the California patients, for example, that enrolled in this study and look for association with perhaps unsuspected cancers. I don't think the yield will be high, but it would be an interesting thing to do because the data would be there.

DR. LoCICERO: Okay. We need to have -- Dr. Whorton.

DR. WHORTON: Just, it seems like we're getting into the Kaiser Permanente. There's lots of huge insurance and non-insurance-based data that a lot of the Federal agencies actually contract to use. And you can build subsets. You get all kinds of studies within that framework, and they should

all be investigated, maybe among SEER being included. But there -- and that's, I think, what FDA's message is. Look at a lot of the databases, at the general purpose, and see if you could piggyback.

DR. LoCICERO: Okay. So we're going to have a -- the next question's on MRI, and then we've got Part 4(b)(4) on MRI screening. So I would like to put that -- and -- with number 5 together. So based on 4(b)(1), (2) and (3), Dr. Marinac-Dabic, have we sufficiently addressed your questions?

DR. MARINAC-DABIC: Yes. Thank you.

DR. LoCICERO: We have one more comment by Dr. Connor.

DR. CONNOR: So, here, I think one thing that maybe we didn't capture during summary, but we heard a lot of, is that especially in studies that aren't registries, but are doctor/patient interaction, is that these postapproval studies were done by sites that were not used to doing clinical research. You know, all of us who do clinical research know the value of a good study coordinator, someone who maintains relationship with patients, and it sounds like that just didn't exist in, you know, the Mentor study in particular.

So if there is, you know, a smaller, maybe more confined postapproval study, making sure that it's done with good clinical sites or places with a good study coordinator will definitely help compliance and follow-up.

DR. LoCICERO: Okay. So let's have Question 5, and we're going

to put 4(b)(4) together with that.

DR. KRULEWITCH: Please comment on the current scientific data available regarding recommendations about MRI screening for silent rupture in the approved product labeling.

DR. LoCICERO: Dr. Glassman, you want to begin again or Dr. Jones?

DR. GLASSMAN: Len Glassman. The current scientific data is that MRI without contrast is the best tool for the evaluation of intracapsular or extracapsular rupture, silent or not. The picture of the ultrasound we saw yesterday was not even in a patient. That was an in vitro image, from the looks of it. And I can tell you, in vivo, it's not that nice. And as I said yesterday, you also can't see around the implant, you can't see the back edge, all things you can see with MRI. So I think that is the best thing.

In terms of the approved product labeling, it is an impossible thing to request patients to do. Nobody pays for it except the patient, outside of the core study. It is expensive. If the patient is asymptomatic and we find a rupture, chances are nobody will do anything about it. Therefore, we shouldn't have done the test in the first place, and I would drop that MRI recommendation from the labeling.

DR. LoCICERO: Dr. Jones.

DR. JONES: Yeah. I completely concur. The asymptomatic people really don't need -- they aren't doing it anyway, and I think, in the core

study, the rate was so low, it also -- that just reinforces what we already thought. For symptomatic patients, it's different, and absolutely, you know, they should continue to get that, especially if you're going to explant and then, you know, really, what you're -- you've got good proof of it.

I think it was -- if I understood Mr. Melkerson yesterday, it was added in the hopes that you would have some sort of clarity as to whether an implant had ruptured at some point when patients maybe later developed some abnormality. And it's just -- you know, as Dr. -- sorry -- Glassman said, it's just impossible and people aren't really doing it, so I would just drop it.

DR. LoCICERO: So of the patients who are going to -- the recommendation is going to be made that they have an MR, what are the impediments to getting it done?

DR. JONES: Well, I think it's mainly the cost. It's not a particularly fun exam, and some patients, you know, find it uncomfortable. It's not that long, but it's usually a bit uncomfortable. You know, you've got to take time out from your work and so forth. And mainly it's just very expensive. Also, some people really don't want to know. Why would I want to know? If it could be a false positive, I don't want to be explanted or being worried that I should be explanted when it's actually normal, for instance, because it's not a perfect test. Nothing is. So I think there's, you know, some real obvious reluctance for people to go through with that, you know, what they perceive as unnecessarily.

DR. LoCICERO: Dr. Hennessy.

DR. HENNESSY: Sean Hennessy. So my question is, if all the hundreds of thousands of women who are getting breast implants got -- tried to get screening as recommended, is there enough spare capacity in the existing MRI system to handle it?

DR. GLASSMAN: Currently, no. However, this is a capitalist society, and you would see MRs popping up all over the place if there was a need.

DR. JONES: If you come, we will build the MR.

DR. HENNESSY: The -- I would imagine that the price per quality-adjusted life-year saved by a strategy of screening was probably pretty high.

DR. VEGA: Some people have a phobia or a fear of a closed MRI, and that does enter into a very important part for patients.

MS. MATTIVI: Kris Mattivi. I think if there were evidence that -- with a rupture, that the extruded material posed some health risk to the patient, that that would be a compelling reason to go ahead and get an MRI to rule out the possibility of a rupture. But with the lack of hard data to show that there is a health risk if there has been a silent rupture, I think that just reinforces the why bother.

DR. LoCICERO: Dr. Whorton.

DR. WHORTON: I completely agree. And somebody said earlier

that at a point, it becomes -- it's not a physician problem. It's a people problem. They become humans and not patients. And I think the long-term studies were really trying to find out what we need to find those -- out about those people as patients -- I mean as people. And it may be a different kind of dataset, less extensive maybe for the long-term human kinds of studies than the more intensive early studies, particularly ones where they need maybe an MRI before an explant.

My question is, in the studies, without an MRI, do we expect to be able to get a reasonable read on the signs and symptoms that would give us a good snapshot of the difficulties associated with implants, or would we miss a lot of signs and symptoms and complications without an MRI?

DR. LoCICERO: A radiologist maybe should answer that. Okay. Dr. McGrath.

DR. McGRATH: As a clinician, I think you can emphatically say no, you would not.

DR. WHORTON: Good. That's what I thought.

DR. LoCICERO: Ms. Dubler.

MS. DUBLER: I have a -- first of all, I have a fear of small places, and so it would be incredibly unattractive for me to face an MRI on anything more than my knee, which I have had. But it does seem to me that the indications for MR that have emerged from this discussion are interesting. So someone said -- I forget who -- that if you're having an implant removed,

that's in an indication from -- for having an MRI before it's done so that the surgeon really knows what he or she is facing. Is that correct?

DR. LoCICERO: Go ahead.

DR. GLASSMAN: Len Glassman. I think, in the context of remove because you think it's ruptured, that may be correct. Although there are -- and I put down ultrasound. There are some ultrasound signs, when you see them, are very specific and very accurate, and I think you could go ahead. But if someone thinks it might be ruptured and let's go find out by operating, that's when you would want to get an MRI to see what's going on, but if you wanted to get an -- you wanted to be explanted because you wanted a bigger one, no.

MS. DUBLER: So it would seem to me that it would be worth it for the FDA to find out, to make a list, a finite list of those times when an MRI would be recommended. You've given one. And what I don't know is some of the women who spoke talked about generalized malaise, and I don't know if there's any way to capture that. I mean if your health is a disaster and you've got an implant, consider the implant. I mean how do we capture knowing that the plural of anecdote is not data? How do we capture the things that we've heard in a way that tips off the surgeon and the woman to when this might be necessary?

DR. LoCICERO: Dr. Glassman.

DR. GLASSMAN: Len Glassman again. One thing about the first

thing you said, and that is the FDA is not in the business of practicing medicine, and they, I think, would agree with me that they are not in the business of making lists for when patients and doctors should do things.

MS. DUBLER: But they do approve the labels, and my question is, what part of this discussion -- the labeling now says get an MR every two years. Is that what it says? Three years. If that's going to be removed, what replaces it? And yes, I'm not -- I don't think the FDA should practice medicine, but there are a lot of people with a lot of knowledge who do practice medicine, and perhaps their knowledge needs to be reflected in whatever the label says.

DR. LoCICERO: So, Mr. Melkerson.

MR. MELKERSON: First, a little historical. I think we were trying to answer the question of which came first, the chicken or the egg. Were the symptoms that were being seen related to either gel bleed or rupture, and MRI was definitively, at the time, the most appropriate way to detect silent rupture. In terms of our current position, we have not seen data to counter the fact that we know the implants do rupture and do have silent rupture. So -- and they do increase over time. The question that the large studies were trying to address and put to rest were the associated symptoms being described, you're describing was the anecdote. Were they indeed related or not?

So we're in a quandary here of, which comes first, the chicken

or the egg, the symptoms or the rupture, and what's the best way to assess that? So when you're talking about MRI and saying, well, if we don't see any symptoms, then we don't look for the MRI, there are cost-prohibitive issues. There may be other things to consider in terms of maybe at different times, and I think you're touching on some of those. When is it appropriate to do it or not? We don't have that answer, so how do you answer that question?

DR. LoCICERO: Okay. So it really does bring up the point that we need to get to here, and that is, does the labeling need to be modified. The recommendations that are currently there, one at three years and then two years -- every two years after that, those need to be removed, does it need to remain the same. Thoughts about that? Dr. McGrath.

DR. McGRATH: I would --

MR. MELKERSON: Excuse me. Chair, may I interrupt? This is related -- the question is related to the postapproval studies, not the labeling of the existing products.

DR. LoCICERO: Okay. So we'll just drop it and leave it to everyone's imagination what we would say.

So are there other comments concerning postapproval studies? That was not included in this question, so it confused me. We've commented on the current scientific data available regarding the recommendations about the MRI screening for silent rupture as it is stated in the approved product labeling. So have we sufficiently answered FDA's questions concerning this

question? Dr. Marinac-Dabic, have we answered your concerns?

DR. MARINAC-DABIC: For this question, I think everything is addressed.

DR. LoCICERO: So we have three more questions. I think we can take a short break at this point. The -- it's now 2:45. Be back at 3:00 for the last three.

(Off the record.)

(On the record.)

DR. LoCICERO: The last questions that exist, so I would like to ask that Dr. Krulewitch begin with the sixth question.

DR. KRULEWITCH: Please discuss whether the following conditions of approval, in addition to clinical studies, are recommended to evaluate the postmarket safety and effectiveness of new devices in future postapproval studies. This would include:

a. The non-clinical informed decision process;

b. Device failure studies;

c. And the focus group.

DR. LoCICERO: Before we go into that, I just want to ask a question about (b). When you say device failure studies, do you mean free clinical device failure studies or clinical device failure studies?

DR. KRULEWITCH: This is the device failure studies as described in the -- as the condition of approval device failure studies that are associated

with devices returned to the manufacturer after marketing. This is the postmarket condition that we had.

DR. LoCICERO: Okay. So the postmarket condition where the retrieved prosthesis is evaluated for failure -- modes of failure, et cetera, correct?

DR. KRULEWITCH: As a formalized condition of approval.

DR. LoCICERO: Okay.

DR. KRULEWITCH: We -- not talking about expecting that to occur as a routine process.

DR. LoCICERO: Okay. Great. So anybody want to begin with informed decision process studies? Should this be included in other postmarket approval studies as time goes forward? Dr. Hennessy.

DR. HENNESSY: So I think there should be some consistency across products regulated by FDA. There are lots of products regulated by FDA that seem like they would need informed consent. So can you provide us with other -- with information about whether other FDA-regulated products requiring informed consent have required studies of that informed consent?

DR. MARINAC-DABIC: The short answer is no. We have not asked for any other study to be -- for any other device to have a formal study with the informed consent.

DR. LoCICERO: Follow --

DR. HENNESSY: Given that, I guess I don't -- I wouldn't feel

strongly that one is needed here.

DR. LoCICERO: Yes, Dr. Honein.

DR. HONEIN: Well, I would disagree. I think it's actually very important in this case because, in the majority of these surgeries, it appears we're talking about an elective procedure, perhaps 300,000 of the 380,000 a year. So I think informed consent is a much more critical issue, and I was concerned about the results of this postapproval study, that it wasn't being done very consistently. So I think there is a difference from when you're treating a clinical disease versus having elective surgery.

DR. LoCICERO: Yes. The FDA wants to make a comment.

MR. MELKERSON: Just a clarification. Informed decision and this context was, it was required -- or not required. It was suggested that each patient receive the patient information, and it was intended that certain sections be signed as an acknowledgment that you understood the risks. And slightly different than informed consent regulations. It was basically an acknowledgment that you were informed of the -- given information to make a decision, but it wasn't -- it's not deemed informed consent in the study sense.

DR. MARINAC-DABIC: One more point of clarification. For all our postapproval studies, we do require informed consent to be signed as a part of the study, but there is not a specific study that evaluates that. That's important. And it's also important to recognize that these are approved

products and the -- you know, the content of the informed consent is certainly different in this context than it is in the context of the investigational device. Primarily what isn't deemed informed consent speaks to additional risks as being part of the research study rather than the risks associated with the procedure itself.

DR. LoCICERO: Okay. So this raises a -- yes, Dr. Vega.

DR. VEGA: Hi. I would like to take that a step further. I concur very much with what you said. I think it's very, very important, and I caution patients, especially when they've just come out of surgery, vis-à-vis, they've been diagnosed with cancer, et cetera. When they go to make a decision and they have this with them, I suggest they take a tape recorder and/or as well as someone who not only speaks English, but -- or if they're English-speaking, a friend, relative, somebody so -- because you miss a lot.

When you hear the diagnosis of cancer, no matter how much we want to be sophisticated, somewhere, that equivalent is to death. And so, you really don't hear all the details, and you can read the informed consent a little bit, digest it, read a little more, but very often, you miss pieces. So I think this is a very important thing and standardizing it in some way. Some people talked about an hour, an hour and a half where they give preps. Some people may not be able to do that, and I think that's very, very, very important for the patient.

DR. LoCICERO: Okay. But we're talking here about a study of

the informed consent, of the informed decision process which essentially goes through the booklet and looks at it from page by page. I understand your point. So in talking about that, are there other studies that we can look at that have precedent about acknowledging that one has seen and read it and then, later on, testing that information?

MR. MELKERSON: Other than the two breast implant studies, I think there are one or two other examples, but there are not many. It's basically device-dependent.

DR. LoCICERO: So what makes this -- I'm going to ask Ms. Dubler specifically.

MS. DUBLER: If you broaden the category a bit, there are huge numbers of studies that demonstrate: one, that patients don't understand what they read; two, that they don't say that they don't understand what they read; three, that they sign that they do understand what they read; and four, they don't remember what they read the next day. So if you want to -- and that's a little bit cynical, but not a whole lot. So my question is, what's the point of doing this, especially if it's just, you've received it and you understand in the context of something that someone wants? So I would argue that that doesn't really interest me.

What does interest me is how a physician relates to a patient in an elective, cosmetic procedure, and if that's any different than the tenor of the relationship in, here, you have appendicitis, here are the risks and

benefits of surgery in appendicitis. If you don't have the surgery and your appendix ruptures, you may die. You know, there's a lot of grounding in most of the informed consent discussions that take place, but in elective surgery, I just don't understand whether or not there's a conflict -- and I honestly have never seen anything on this -- between the physician who must, on the one hand, be very clear about the risks and, on the other hand, whose income depends on the consent. And I just don't know how or where physicians who do plastic surgery are and how visible that conflict is.

And at the break, I was being told that there are now dermatologists who implant silicone gel breast implants in their offices, which freaks me out totally. So that would be an issue that would interest me as much to raise the level of awareness of conflict as to explore the actual conflict.

DR. LoCICERO: I'm going to add to that. If one has a selection of procedures that can be performed for the same diagnosis selectively, is there any difference between that discussion and what we're talking about here? And if there is no difference, are we really asking that all informed consent be evaluated and retraining surgeons? So maybe this is something that's beyond what we can do. Dr. Connor.

DR. CONNOR: So yeah, I think that's my concern. There's clearly the potential for conflict of interest. The more surgeries I do, the more patients I convince to do this to, the more money I make, and we all

have mortgage payments and alimony, right? But it seems like, you know, the result of this is policing the practice of medicine, which is neither FDA's job nor do you have the ability to do even if you see that no one is watching. So it seems like it doesn't matter what the result of the study is, FDA can't do anything about it and, therefore, I would say we don't need to do it or someone does, but it's not FDA's job.

DR. LoCICERO: Dr. Leitch and then Dr. --

DR. LEITCH: I mean this is --

DR. LoCICERO: -- McGrath.

DR. LEITCH: This is -- there are plenty of other avenues that guide surgeons about proper consent and the issues related to that. And you know, as a surgeon, you know, you don't want anybody laying down for surgery who's not informed and wants to be operated on by you and has to understand what you're doing. And we make a lot of efforts to -- you know, to make that clear to patients. All these things are true.

You can tell a person all the complications that can possibly occur and you've said that and people have witnessed it, and then, the next day, the patient can ask you about something that's happened and you go, well, you know, we discussed that. That's always true, but the -- but for the FDA to change that for all surgical procedures -- because, essentially, that issue exists for all surgical procedures, okay? That a patient can misunderstand or not feel properly informed despite efforts of the surgeon.

So if you're going to do that, I think you would have to do it for any device that's implanted. I mean you would have to say FDA is going to take this on for any device, and I just don't think that's really the purview and it needs to be addressed, you know, in a -- I mean, part of what we do is teaching surgeons how to take care of patients, is proper consent.

DR. LoCICERO: Dr. McGrath, any comment?

DR. McGRATH: Just very similarly, that you're -- I think Dr. Dubler is talking about cosmetic surgery, but there's also a thing called elective surgery, which happens in every specialty. When an orthopedic surgeon decides to put in a knee instead of injecting the knee with something, that's an elective surgery.

So I think that this distinction nowadays is much less clear than it was 30 years ago when there wasn't as much elective surgery. Nowadays, I think that what we do in plastic surgery may touch a little more on quality of life, but maybe it even doesn't, and these lines have become much more blurred. I agree with Dr. Leitch. It's something that, as you know better than anyone, the definition of informed consent is not just risk and benefits. It's also what will happen if you don't do it, and that is clearly something that plastic surgeons make clear to people that, if you don't do this, you know, here's what it will be. So you're not -- if you really are doing informed consent the way we train our trainees to do it and the way we define it, you know, in biomedical ethics, then you are indeed covering those bases for

elective surgery, as well as for emergency surgery.

So I don't -- what I don't understand about this question and I need maybe some help with this, Dr. Melkerson, I don't quite understand what you're asking here. In future postapproval studies, should there be studies of how you get informed consent? Is that what the question is?

MR. MELKERSON: Actually, the postapproval study requirement, and I'll defer back to OSB folks, but my read of the letter was actually how effective was the conveying of the risk and benefits because they surveyed the surgeons and the patients after having received the informed decision-making materials.

DR. McGRATH: And what was the point of it? I mean why were we doing that?

MR. MELKERSON: I think we were trying to address some of the concerns that were brought up in the public comments where I did not understand the risk associated with -- or did not come across, and again, that also goes back to the focus group questions of making sure that people were getting informed of the materials and they understood it.

DR. LoCICERO: Dr. Mount.

DR. MOUNT: We could spend the next week talking about informed consent and all of the patient education issues and strategies. I think that this is definitely an important topic. I think that this is well outside the reach of the FDA, as well as almost impossible to answer because, as

Dr. McGrath pointed out, you know, what exactly is the question as far as the informed consent goes.

The other comment that I would say is informed consent documentation, whether it's the consent for the procedure or consent for an implant, even if it's a temporary implant, all of those documents and requirements are very different depending on which state you are in and also completely different even within the same state of which institution you're in, whether you're in your private office, whether or not you are in an academic center like I am, or even within two different aspects of the same academic center. So I think that this is an area that cannot be answered easily.

DR. LoCICERO: So I think we've pretty well answered (a) here, that no; (b), this is after devices have been removed, the companies were asked to evaluate the device in specific ways. So should that be something that should be included in future studies? Dr. Galandiuk.

DR. GALANDIUK: I think definitely, and one thing I was disturbed about -- I forgot the gentleman's name was. I think it was Dr. Melmed that spoke yesterday, and I was a bit disturbed that -- I know those patients that he was operating on weren't necessarily part of the study, but he was saying all the devices he removes, they're not sent anyplace. They're just given to the patients or that. I mean I think any prosthesis that is removed should be returned to the company for evaluation. And I don't know if there's any way to enforce that, but that struck me as horrible, and I

think device failure studies are very important.

DR. LoCICERO: We used to give the foreign bodies to the kids when they removed from their throats. Now I don't think we do that anymore, but that's sort of the same idea here. Dr. Mount.

DR. MOUNT: First, yuck. But I think that the device failure studies are very important to continue for multiple reasons. And one of the inquiries I made yesterday was about, you know, what sort of information do the companies actually use or -- you know, with this. And obviously, as demonstrated from the companies yesterday, they do glean a lot of information, both in product design improvements as well as in training, as in showing the implants that had been damaged due to operator error, and then had made subsequent teaching and training improvements. So I think that this really has value for improvement of devices as time goes on, and I think that the device failure studies should continue.

DR. LoCICERO: And as Chair, I'm just going to take the privilege of talking specifically about some of this. In some devices that I have used, it opens a dialogue with the company. As long as you have a receptive company, the dialogue concerning the device helps to determine whether it was the failure of the user, failure of the way it was prepared, failure of the way it performed on the individual, et cetera. So I think that's all very important. So as long as the company is receptive in looking at this in an appropriate way, and maybe the best way to do that is through failure

studies.

Additional comments? Dr. Leitch.

DR. LEITCH: And that's -- again, that's another element in registry. You know, if you have the device registered, you know, as for the warranty thing and then you have -- when it's returned, you have another element within the history of that implant to be able to make comments about how many fail and this sort of thing. If they're never returned, there's no way to know that information. So I think it provides ongoing information, as well as all these other things that were talked about in terms of product improvement that can help.

DR. LoCICERO: So, Dr. Galandiuk.

DR. GALANDIUK: And I think what's very important is, many times, patients don't go back to the same surgeon, so you can't use the TOPS data or something like that to get that data because patients will frequently go to another surgeon.

DR. LoCICERO: All right. So I think our feeling here is, not only yes, but yes in spades, and it ought to come with a club. How about Dr. McGrath?

DR. McGRATH: I was okay with yes. I'm even okay with yes in spades, but you can't put a club on it because a lot of hospitals, particularly the major medical centers, won't give you clearance to send the device back to the manufacturer.

DR. LoCICERO: And give us a little more expanded on that.

DR. McGRATH: Well, when you remove a foreign body, the -- it becomes a property of the pathology department, and for a lot of reasons, they want to have access to it.

MS. DUBLER: Well --

DR. LoCICERO: Ms. Dubler, any legal reason why that would be the case?

MS. DUBLER: I would have to look at the terms and conditions under which the physician who received -- I'm really startled. So the pathology department would override the general conditions of care understanding?

DR. McGRATH: Well, in general, what happens is, in any operating room in an American hospital, pursuant to Joint Commission regulation, there has to be a thing called the Tissue Committee.

MS. DUBLER: Right.

DR. McGRATH: Tissue Committee legislates exactly what has to be submitted to pathology for evaluation when it's removed from a patient and they all have retention policies. Those vary from place to place, state to state, hospital to hospital and there are -- so you -- I don't want this to become something that is written in stone because it would be very difficult for some people -- some surgeons to be able to bring this -- put this into place in their institution.

MS. DUBLER: Although --

DR. LoCICERO: All right.

MS. DUBLER: -- it would be worth their efforts to try to change the policy to be in line with the national norms.

DR. LoCICERO: So I agree with you in terms of yes, there are local issues, and they do vary, sometimes within the same city, and a lot of that is due to the archaic pathology departments that really can't -- have not moved along. And yes, I have dealt with this personally in institutions and seen it, so you're right. It's probably a bigger issue than we can tackle or the FDA can tackle right now, but is a major problem.

Any other comment about that? Yes?

DR. GALANDIUK: Susan Galandiuk. I think a lot of that is based on litigation fears, mainly for retained foreign bodies like sponges and things of that. I think for a medical device, if there was a concern raised about device failure, I think almost every pathology department would give an exemption to that.

DR. LoCICERO: As long as the chain of evidence is maintained. So, Mr. Halpin.

MR. HALPIN: The only thing I wanted to mention is that's actually a GMP requirement to do explant analysis on returned materials. So I think when you think of device failure studies, as proactive as this, it's when there's a sense of urgency about understanding it and you want to make sure

you capture as much as possible, so you want to proactively pull from the study in order to understand it in a more meaningful way because, as you can see, there's a lot of passive reasons why things may get delayed or not show up on time. But it is a requirement to actually do that when you receive those.

DR. LoCICERO: And, in fact, one of the ways to approach this on a Tissue Committee is to force the issue of reporting to the MAUDE database, which would then require that the device get sent back.

Okay. Focus group. Should there be a focus group attached to postapproval studies in the future? Let's begin with Ms. Mattivi.

MS. MATTIVI: Gee, thanks a lot. I think if there is enough concern on the FDA's part to require a postapproval study because of concerns that were in the premarket approval, that certainly a focus group that included the consumers' point of view would be very important.

DR. LoCICERO: Other comments? Yes?

DR. CALLAHAN: I agree. I think we gather a lot by sort of mixed methodology and having qualitative data and quantitative data, and we've seen, sort of, the lack of information we got from some of the quantitative data because of the loss to follow-up. And it's not a huge expense to add focus groups to studies, so I think it would be a valuable requirement.

DR. LoCICERO: Mr. Melkerson.

MR. MELKERSON: Just to help focus, this came from the

approval orders. When we're talking about a focus group study, they wanted involvement of a group to obtain responses from patients on format and content of the approved labeling. Upon completion of the focus group study, provide a supplement with a report of the focus group studies and revise patient and physician labeling based on those findings. So if that helps formulate your discussion.

DR. LoCICERO: So this was specifically to review the labeling and whether or not the focus group was happy with labeling and with the wording of the labeling, I take it. So -- yes?

DR. HENNESSY: All right. So has that been done and is your question now, should it be done again? I'm trying to figure out the context.

MR. MELKERSON: Again, we're -- these are for future studies. This was done in the previous postapproval studies for the two approved PMAs.

DR. HENNESSY: Right. So if -- and this is assuming that there would be new labeling. So if there is a revision of the labeling, should the labeling be tested again in focus groups? Is that the question?

DR. LoCICERO: Well, I think the way we understand it, this would be for future studies --

DR. HENNESSY: For future studies of future products or future studies --

DR. LoCICERO: Future --

DR. HENNESSY: -- of these products?

DR. LoCICERO: Future products. Future products.

DR. HENNESSY: Future products. Okay.

DR. LoCICERO: Dr. Mount.

DR. MOUNT: I think our companies proved that this is actually a helpful study group to sit with, particularly when Allergan showed the BIFS and the change in the label and the way mailings happened and things like that, which were a lot more receptive for patients and particularly for privacy issues. So I think that they wouldn't have had that information had they not had their focus group, and I think that they showed that that's a worthwhile thing to do.

DR. LoCICERO: Dr. Connor.

DR. CONNOR: So I agree that it's valuable, but I'm not -- I don't understand at this point given there are devices in the marketplace again, you know, that you understand labeling about why it would need to be mandated. I agree it's a good idea for a company, and I would hope future makers would do this, but I don't see a particular reason why it has to be mandated by FDA.

DR. LoCICERO: Dr. Jones.

DR. JONES: Yeah. This is a question for the FDA staff. If you look at all the Class III devices, for instance, should there be consistency in whether they all ask for these types of sort of sub-studies in their postapproval studies? Is it totally device, you know, dependent or would a

manufacturer wonder well, why are our devices so much different than some other implantable device and I'm asked to do these other studies? Or are these done in those other devices as well?

MR. MELKERSON: Short answer is each PMA device has to stand on its own, so whether or not their labeling is appropriate may be a -- it may not be just be device type. It could be one manufacturer's labeling is okay and then others may not be, but the issue is they have to stand on their own. So the question as being asked here is, for future studies, future devices, is this a viable option for breast implant manufacturers?

DR. LoCICERO: Dr. Crouch.

DR. CROUCH: Barbara Crouch. I think it is. I think what was shown is the company's got valuable information to modify, and I think because this is, again, a lot of the individuals are doing it for aesthetic purposes, then I think the better you can modify the labels with clear language, with the risks and the benefits, I think that will go a long way. So I would encourage them to continue.

DR. LoCICERO: Dr. Glassman.

DR. GLASSMAN: Len Glassman. I also think it's a good idea. However, if the labeling on the new device is essentially the same as the labeling on a device that has already been through a focus group and is in the market, I see no reason to repeat the study.

DR. LoCICERO: Dr. Honein.

DR. HONEIN: Peggy Honein. So I just wanted to concur. I think the value of the focus groups that were done was shown in the materials that we were given. One suggestion: if there are future labels that this was undertaken for, at least as I read the information, it looks like they did it in sort of the four, straight up, primary augmentation, primary reconstruction, which makes sense. But typically, for focus group research, you would do at least two focus groups for each of those strata, and it didn't appear that's what happened. So I think, for marginal, additional expense, there could have been even richer information gathered, and I think this is a very helpful avenue to understand how the labels are being comprehended.

DR. LoCICERO: So to summarize, we think it's a good idea, relatively inexpensive, and may actually help to engage the stakeholders.

So concerning Question 6, Dr. Marinac-Dabic, have we answered your concerns?

DR. MARINAC-DABIC: Yes. Thank you.

DR. LoCICERO: Thank you. Question 7.

DR. KRULEWITCH: Just to refocus, these questions are specific to silicone gel-filled breast implant postapproval studies, not all devices. Although, I'm -- I just want to make sure we keep the questions focused on the topic of the day.

So in future postapproval studies of other breast implants -- and this question will divert just slightly -- that utilize the same technology as

implants already approved, please discuss:

a. What postmarket evaluation is needed for newly approved breast implants that are similar to currently improved implants on the market?

b. How should new styles or procedural techniques of the same technology be incorporated into ongoing, mandated postapproval studies?

And all of this does refer to mandated postapproval studies, not just postapproval studies in general.

c. And what are the most appropriate comparators, if any, for an nth generation, or a breast implant that's more than three or four generations down the line, of the same technology?

DR. LoCICERO: Okay. So for clarification here, are you just hypothetically talking about similar devices, but not similar enough that they are -- because they're not similar enough, that they require a PMA, or are these all devices whether they get a PMA or they get into the market through a 510(k) mechanism?

MR. MELKERSON: They'll all be PMAs.

DR. KRULEWITCH: Yeah.

DR. LoCICERO: Okay. So although you're saying they're similar, there are sufficient difference that it requires a PMA to get approval?

DR. KRULEWITCH: Right.

MR. MELKERSON: Or they're a different manufacturer.

DR. KRULEWITCH: Or another -- yeah. Another manufacturer --

MR. MELKERSON: Or another technology --

DR. KRULEWITCH: -- of the same.

MR. MELKERSON: -- that raises new types of safety and effectiveness questions.

DR. LoCICERO: Okay. Is everybody clear on that? Yeah, great. Okay. So if I -- if pens are on the market and I make a new pen and it's green, but it looks like this one, then I can get in by a 510(k) mechanism if we were approving pens, but if I change the cap and the cap is sufficiently different, that it now flips and works differently, then that is going to require an additional study to get approval so that I can sell it. Is that a little more clear?

MR. MELKERSON: With the exception of the 510(k) analogy, yes. Under a PMA, it would be a PMA supplement --

DR. LoCICERO: Okay.

MR. MELKERSON: -- and that would typically be one manufacturer making a minor modification to the device that didn't need a new clinical dataset.

DR. LoCICERO: Okay. But if I were a different company making a green pen that looks exactly like the black pen?

MR. MELKERSON: They would still need their own PMA because it's a Class III product.

DR. LoCICERO: Okay.

DR. WHORTON: So if I had a product that we used to spray mosquitoes and then I wanted to slightly change the color to put it on humans, the color may not make a difference, but the shift would, and it may require a whole different process.

DR. LoCICERO: Correct. So --

DR. WHORTON: Correct? Okay.

DR. LoCICERO: Yeah. So --

DR. WHORTON: That was the --

DR. LoCICERO: -- if there's sufficient difference, it requires a PMA for whatever reason. It gets approved, then we're going to do postmarket studies, okay? Pretty hypothetical here. Ms. Dubler.

DR. WHORTON: Would it require premarket studies?

MS. DUBLER: Too hypothetical for me. It seems to me -- I love hypotheticals. You've all seen that. But it seems to me that whether there are postmarket -- postapproval studies that will be needed, and what they are will be directly related to the testimony at the PMA hearing, and I don't see any way this Panel can give any useful comment on this question.

DR. LoCICERO: Dr. Mount.

DR. MOUNT: I agree. This is way too hypothetical. If the

device is different enough for whatever reason that it requires another PMA, how would that be different than a completely new device that is not even a breast implant that goes through a PMA? We can't advise on postmarket issues, as far as that goes. But let's keep it with -- and I see Mark Melkerson wanting to correct me there. But if it's different enough that it requires a PMA, it's very outside our realm of hypothetical to recommend what those post -- what those PAS studies should be or what they should be mandated.

MR. MELKERSON: Let me see if I can clarify her general hypothetical. It's another silicone breast implant similar to the two that are currently approved, but by another manufacturer, that requires its own clinical dataset.

DR. MOUNT: This is Del Mount again. Why would it require its own if it is exactly the same?

MR. MELKERSON: That's the -- as a manufacturer, if you want to market a product, you have to go through the same threshold of data for your product to get a premarket approval. The question then is, if you've had to go through and collect your own dataset for premarket approval and you're now coming up on postapproval study issues, do they need to answer the same questions existing? And we have, over time, and I'll use orthopedic implants as an example, once you get past the first, second, or third, do you still have the same questions or not?

DR. LoCICERO: Dr. Connor.

DR. CONNOR: Yeah. I think the -- I guess the question -- the open questions are the open questions, but they're not product specific, right? It's not whether Lucky Strike cause cancer or Marlboros cause cancer. It was, did smoking cigarettes cause cancer. And so it's if this is the same product with a different manufacturer. So does the case cause connective tissue disease, does silicone leaking cause lupus, does --

So I think given -- we've said registries and population-based things are the best ways to answer that, combining currently marketed products with these hypothetically new products coming on the market. That data should be combined, you know, maybe using statistical methods that realize there's heterogeneity or the potential for heterogeneity.

But I think we're saying, you know, the new studies shouldn't, you know, need a 40,000 large study because they're not working well here, and we've expressed reasons why, you know, maybe that's not the best reason to open some of the answered questions. So if a new one were approved tomorrow, I would not expect it to go through the same postapproval studies as these two did, nor would they need to because the question is product specific, not necessarily manufacturer specific.

DR. LoCICERO: So just in terms of that too, it's a different company, so they may have learned from the two previous companies and answered better -- answered the questions in a better manner or maybe had better follow-up, maybe tighter datasets that don't require additional

postapproval studies.

DR. CONNOR: Right. And actually, coming into today, one of my fears was that, you know, Mentor did some of their postapproval studies so poorly, and Allergan, you know, not great, but better, that future hurdles would be even so much harder that they would actually derive a competitive advantage because it would be harder to get something new on the market. Thankfully, I have not heard anything of that nature here, but right. So I think, you know, we can learn and, you know, they have the benefit of being first on the market, but new companies will have less of a postmarket hurdle, and I think that's appropriate and okay.

DR. LoCICERO: Dr. Honein.

DR. HONEIN: Peggy Honein. So to the extent that standard protocols can be utilized for future devices so that there can be comparisons made across the studies or pooling of data across the studies, I would certainly advocate for that. And if there are nice approaches such as those that have been mentioned today using the Kaiser data, using SEER data, that the existing two devices uses, then it also makes sense to me that subsequent devices would be evaluated in a similar matter so that comparisons can be made.

DR. LoCICERO: Dr. Leitch.

DR. LEITCH: I think it would depend a lot on what the data is in the PMA and the data that's presented. If it looks a lot better and the data is

presented in such a way that's highly convincing to the Panel, then those studies may not be necessary. If it's -- you know, if it raises doubts, then yeah, there's going to be -- then you're going to -- probably some of the same questions we already talked about as future PASs that we've already mentioned would be what you would pick as the study questions for a new device.

DR. LoCICERO: Dr. Mount.

DR. MOUNT: Well, the whole idea of doing the PAS was to answer questions that couldn't be answered before, or just the data wasn't there or, you know, perhaps the question wasn't even raised yet. If the PAS is completed in one group and that question is answered, then the next group coming down the pike, why would they have to re-answer that question? And then, secondly, what if a new question is discovered? Would you go back and make the newer company come in and answer the newer question?

So I think that with time, the landscape is going to change so drastically, particularly if we get some very good answers from the large study data with the PAS. With the two groups that are current, those questions may not even be applicable or important at the time if other groups come in.

DR. LoCICERO: So I think we can summarize by saying, for Question 7, that we don't feel we want to preempt the future panel which will review that PMA and what recommendations they will have for

postapproval studies, although this can be a guideline for or a framework for them to begin discussion. Does that sufficiently state what we're talking about?

Okay. Dr. Marinac-Dabic, have we answered this question?

DR. MARINAC-DABIC: That question or just (a)?

DR. LoCICERO: No. I think we got them all.

DR. MARINAC-DABIC: All right. So then I have, maybe, a couple of sub-questions, if I may.

I think the -- what was in the core of this question, and maybe to rephrase it in a somewhat different way that I -- colleagues, statisticians in particular will appreciate. It's -- as we move from generation of devices to generation of devices and modifications are being done, then what is the value of really employing the methodologies that will ensure that we learn from the previous experiences? And the knowledge that had been gained in the previous devices still contribute to the knowledge about the safety and effectiveness of the devices that need to come to the market.

And I think that's the basis of this question, that you actually, very nicely, put together. There are some questions that had been answered and can -- one can actually learn from those and then build them and in the -- you know, kind of Bayesian method spirit, really advance the knowledge and focus the new studies on really new questions, not to restate the questions, especially in the device like this when we have these studies when there are

40,000 patients.

So how then did these new modifications, even if they require a new PMA, how you actually ensure that they are captured properly in these, even if we establish the national registry? What are the methods one can utilize that will not necessitate for every new breast implant that comes in market to have additional 40,000 patients or additional, you know, group being looked at to address all the questions.

DR. LoCICERO: Well, again, we don't know what hypothetical new questions will come up concerning the devices, but let's begin with Dr. McGrath.

DR. McGRATH: I guess the only thought I would have is that if, indeed, we did end up with some sort of a concept like a registry that, in effect, has no end term, in other words, it'll be a postapproval study or entity that will go on for an indefinite period of time because it's trying to capture all of the implants that are being used, then I think any new device that comes along should have to fall under that same umbrella and also have to be involved in that process, that registry type process.

But to be more specific than that is very difficult because to preempt someone coming along, let's say, in two months with another breast implant from having to do what these two sponsors are doing is -- doesn't make sense, and it's patently unfair because they're still in the process of trying to grapple with finishing answering these questions. So until that's

settled and we decide what the postapproval study process is going to be, very clearly, whether or not there is a registry, whether it's an indefinite tracking of devices, then I don't think we can make a comment about what other new devices should have -- what their process should have to be.

DR. LoCICERO: Dr. Connor.

DR. CONNOR: So I agree. I mean it's hard to answer, I think, such a vague question, but in terms of -- you know, you mentioned Bayesian, which is, you know, what I do and can speak to, I think CDRH is really one of the leaders in, you know, Bayesian thought and incorporating Bayesian methodology to answer questions. As someone who does Bayesian analysis for a living, you know, you've made my life easier. You've given it credibility that it deserves, and so I think the fact that, you know, CDRH Bayesian guidance and that you have a lot of great statisticians there, well-versed in that, so I think it's hard to answer the vague question, but the fact that you know that these can be used, and I think the fact that the agency is comfortable with the idea of using those methods is great in that you can do the right thing there when the question is more concise.

DR. MARINAC-DABIC: Thank you. Just one comment, that clearly, the Bayesian methods had been used and in many ways pioneered in the regulatory setting by CDRH, but again, with the note that most of these methods are used premarket and think there is still room to actually apply them in the postmarket setting, which had always made much more sense to

me to begin with because you really have much more information that you know about a device based on the premarket data.

DR. LoCICERO: So have we sufficiently covered this question now? We have another point.

DR. HENNESSY: So if the hypothetical new device had the same chemistry in both the silicone and the shell, and the systemic questions about those things had already been addressed, it doesn't seem like a good use of resources to re-answer those, but to rather focus on -- so, for example, if it had a different shape or a different size. Focus on effects that could be due to the differences of the new one rather than the old one.

DR. LoCICERO: Other comments? Dr. Whorton.

DR. WHORTON: Yeah. First, there are many ways to analyze decent sets of data and hopefully to get the same answer. There are very complex ways to handle very complex datasets and very simple ways. It seemed like maybe one question, if there was a registry like Dr. McGrath is suggesting, the question may not be -- and these data, will go into a registry, hypothetically. The question is how much data do you have to have before you make a decision, 40,000, the same as before, or should it be -- could it be something less? And then the comparative groups may be what was on the market before this one. So those are all things that have to be, to me, worked out, but a lot of it's a quality or quantity of data that's a question too.

DR. LoCICERO: Again, always influenced by what's already

available, what data's already available.

Other points? Dr. Glassman.

DR. GLASSMAN: Just one that I've heard that the definition of insanity is doing the same thing over and over again and expecting a different result. I think this may come under that, asking the same questions that have already been answered.

DR. WHORTON: Well --

DR. MARINAC-DABIC: Thank you.

DR. WHORTON: -- we mentioned, the premarket studies should give some insight as to how different the new one is compared to an earlier one. And once you have a feeling, uncomfortable, then make a decision on the postmarket studies --

DR. LoCICERO: I think I heard it, but I was thinking the same thing over here, again. I overheard a comment about insanity, and it's really -- I thought that was the definition of a scientist.

So have we answered this question now?

DR. MARINAC-DABIC: Yes. Thanks.

DR. LoCICERO: Okay. We're ready for Question 8.

DR. KRULEWITCH: Last but not least.

Please discuss the unique contributions that groups other than FDA can make to implement and maintain improvement strategies for current and future postapproval studies of silicone gel-filled breast implants.

DR. LoCICERO: Okay. I want to open this with the consumer groups because I'm -- yesterday, the representative from the National Women's Health Network mentioned that her group was working with the FDA for future situations and Lamaze, which is a member already of the -- is already a partner of MedWatch, I'm very disappointed that the consumer groups came here to bash the process and do not seem to wish to be involved, only except to come here every time there's a Panel meeting and bash the process.

So how are we going to get those people involved in the process to improve it and become a stakeholder? Again, so I don't want to pick on Ms. Mattivi, but can anybody give us some thoughts about that? Dr. Whorton.

DR. WHORTON: A question: Have they ever been invited to become a part of it and under what context?

DR. LoCICERO: Maybe they haven't been, and maybe they should be. Ms. Mattivi.

MS. MATTIVI: Okay. So I'll volunteer this time. I think, when we talk about developing the national registry and what kinds of elements belong in the national registry and how to facilitate enrollment in the national registry, I think those are all very good places for consumer groups to be invited to have their voices heard. You know, focus groups, as we discussed earlier, are other places to invite those kinds of groups to the table to have

their voices be heard and to give their contributions about what they think are important elements to contribute.

DR. LoCICERO: Yes, Ms. Dubler.

MS. DUBLER: I think that some of our discussion today has been about the FDA acting as convener for the stakeholders who are most involved in these issues, be they the surgeons, the manufacturers, and I think the women's and consumer groups. I think that if you do a broad-based stakeholder analysis and in that stakeholder analysis you then plan to involve all of the groups -- and the CDC sort of escaped that stakeholder analysis earlier today, but I suspect they're in there too. And I think you bring them all together and see whether these not very highly powered and impressive studies, which can't just be abandoned because we need the data that they would produce, can be replaced by more broad-based, widely supported studies that will get the data that surgeons and women need.

DR. LoCICERO: I have to say, I'm old enough to have seen the miracle of Government agencies actually beginning to speak with one another, and I think the FDA has actually led the process a little bit there in getting together with the CDC, the NIH, and other governmental bodies. And it's very forward thinking, and I think it's to be applauded.

So, yes. Dr. Crouch.

DR. CROUCH: Barbara Crouch. I think there's an opportunity. I heard from a lot of folks that they didn't use the MedWatch system, but I

don't think it's user-friendly to the lay public. It's somewhat difficult, I think, as a health professional in using it because, from a drug adverse reaction standpoint, it say I only want to hear about severe, life-threatening adverse reactions. So I think there's an opportunity to make it more user-friendly and invite individuals to share their experiences with devices that might then add to the registry.

DR. LoCICERO: And that probably could use a focus group as well. Yes, Dr. Galandiuk.

DR. GALANDIUK: Several years ago, there was something called a Colon Cancer Coalition, which was basically a group of societies that were all interested in colon cancer. And you could do something like a breast implant coalition or something and just invite all the stakeholders to participate, ASPS, the FDA, the Aesthetic Society. Invite the groups, and I forgot the names of all the consumer groups that were there, and have them each have one representative meet in a central place. Have the industry representatives come and just, for a day, discuss how you can increase participation in a registry, and I think you would accomplish a lot.

DR. LoCICERO: Dr. Connor.

DR. CONNOR: Yeah, I agree. The idea of different Government agencies working together is very important here. I know I'm involved in a group where the FDA is working with the NIH and, you know, it's funding studies to look into products that, you know, no company's going to make

much money on, but it would lead to, you know, a study that led to a label that would help the public health, that in particular, and emergency medicine.

So I think, you know, I don't know how these things are initiated where someone at FDA talks to someone at NIH to say this is an important public health question. Obviously, these are, you know, very widely used. And it seems like we have, you know, the professional societies and many other agencies wanting to get involved. So this seems like an important enough question that lots of people are interested in answering and, you know, for instance, the Sherine E. Gabriel studies that were very important coming out of Mayo when this first came up in the '90s, you know, were NIH funded. And so, fortunately, I think there are a lot of mechanisms and people interested.

DR. LoCICERO: Dr. Crouch.

DR. CROUCH: Barbara Crouch. I think the other -- the CDC was mentioned, but the National Institute of Environmental Health Sciences, which I think is part of the CDC, is leading the way in really looking at the epigenetic studies. And so they may be a great partner to talk about looking at some of these genetic determinants and perhaps environmental interaction.

DR. LoCICERO: Dr. Glassman.

DR. GLASSMAN: Len Glassman. There are three specific

recommendations from the radiology community. One is ACRIN, the American College of Radiology Imaging Network. That was the group that did the DMIST study with the NCI. The other is the American College of Radiology Breast Imaging Section and the Society of Breast Imaging. These are all groups that I think would welcome participation and may be helpful in looking at alternative ways to do studies or doing studies outside the manufacturers to answer general questions rather than specific device questions.

DR. LoCICERO: So are there any stakeholders that you would -- Mr. Halpin.

MR. HALPIN: Just wanted to mention that, we've looked at a lot of registries from outside the U.S., so rather than thinking of just U.S. or Government agencies within the U.S., there's a Danish registry, a Swedish registry, British, Australian. And the other is there's a lot of biomaterial societies that might be interested in getting involved in this to a certain extent as well from a biomaterial point of view.

DR. LoCICERO: Excellent point. Are there any organizations, individual societies, agencies that you would decline to include if they called up and asked to be a member at the table? So if somebody -- if there was a group of individuals that were interested in this and they wanted a seat at the table, they could get one. Is that what we're saying? Yes.

DR. GLASSMAN: I would say the Society of Trial Lawyers should

be exempted.

DR. LoCICERO: No comment.

DR. LEITCH: I think it would be, you know, what they bring to the table, you know? Do they bring a constituency? For example, if you're looking for an organization to help you accrue patients, well, do they bring a constituency that they can influence to participate in trials? So it has to be, they -- you know, they have something to contribute to the discussion, not just to be negative or whatever, but they have the potential to provide assistance.

DR. LoCICERO: Dr. Honein.

DR. HONEIN: Peggy Honein. So as a Government employee, I think I can say that, you know, a certain amount of potential participants have some skepticism of the Government. So I think, when I look at this question and it says groups other than FDA, I do think that, for some future postapproval studies, thinking of non-Governmental organizations and not the sponsor organizations, but some perhaps academic or other independent group might be more appealing to participants because there can be a certain amount of skepticism if they feel like a role that they may not see as appropriate for Government or that they have concerns about the Government's involvement in it. And similarly, obviously, the sponsors wouldn't be disinterested third parties. So I think this just offers an opportunity for us to think outside the box of how to do these.

DR. LoCICERO: So there is one more issue here, and that is, we're talking about future postapproval studies. So the soonest that could happen would probably be, let's say, hypothetically, next year because I don't believe you have anything on the docket. There are no applications for new devices, new breast implants at this point, are there?

MR. MELKERSON: Wouldn't be able to tell you if we did know.

DR. KRULEWITCH: The word current is in there.

DR. LoCICERO: Okay. Great. So I think that's important because then that tells us that, in terms of timing, should this happen soon, should this wait until there is another PMA before a Panel, before a group like this is convened?

MS. DUBLER: I actually think there's some urgency to the matter because the -- I think the consensus of the group, and please yell if I'm wrong, is that the studies being done by the two companies are clearly and deeply inadequate, that despite what we say, they probably can't do better. I mean I'm sure they could do better, but it doesn't seem to be worth the effort when developing a new structure might get us much better data than we could if we pursued this early foray. And therefore, I mean, my sense is that the FDA needs to move ahead with some speed to be able to create the coalitions we're talking about that can do the work that clearly needs to be done.

DR. LoCICERO: Dr. Mount.

DR. MOUNT: Well, I think the testimony that we had earlier today, both from the ASPS and ASAPS and the ASERF committees, were very key. And particularly, the thing that was very striking to me was Dr. Puscic and the fact that, even though this data that has come out recently about this possible connection with the ALCL, already the Committee is formed. They're ready to study. I think that the addition, particularly the large stakeholders like ASPS and ASAPS, really adds a degree of agility and responsiveness and faster sort of culmination and attention to that data than what, perhaps the manufacturer or definitely, the FDA can provide. I think that it's excellent to have them in as part of the stakeholder share.

DR. LoCICERO: Ms. Mattivi.

MS. MATTIVI: Kris Mattivi. I was going to absolutely agree that the groups that came to the podium today were obviously very interested and very willing to jump into the fray and to offer their data, to offer their assistance to FDA. I think from our experience on the CMS side and the QIO world, getting a stakeholder group like that together is going to take a year anyway to get everybody in the same group together and to get that group to come to the consensus and to have an agenda to move forward with. It's going to be a very time-consuming process.

DR. LoCICERO: Okay. So we're sort of saying that this should happen and should happen as soon as feasible. Does this answer the FDA's question, number 8?

DR. MARINAC-DABIC: It does. And I just would like to state that what you heard today from the society is something that essentially talks about the work that had been done with them. We have been interacting with them. Just for you to understand that there have been a series of meetings, participation that already had taken place. The same goes for both societies, as a matter of fact, and that culminated in the CRADA where the society to actually look at the ALCL issue. And we certainly look forward to expand this collaborative work because we value the contribution and we know that we cannot do that on our own. So it's absolutely -- we do recognize that need and certainly we are happy that the Panel came up with a strong recommendation to do the same.

DR. LoCICERO: Thank you. So are there any additional summation comments that you would like to make?

DR. MARINAC-DABIC: I just would like to thank the Panel. This is actually our first postmarket Panel to address these type of issues, and I cannot tell you how -- for an epidemiologist and a physician, how wonderful it had been to listen to colleagues that have the similar background and also enriched with the colleagues that have clinical experience and also consumer and industry and patient representatives. I think it's in line where we are moving with regard to these future studies.

Again, I would like to thank you again for a very productive two days and for great recommendations. There are many of them that can be

immediately implemented. Some of them may require a little bit more work, but we are committed to move forward as quickly as we can. Thank you.

DR. LoCICERO: Thank you.

Mr. Melkerson, any comment?

MR. MELKERSON: I would just like to echo the thanks for the Panel for putting up with our vague, future questions, but every once in awhile, we try to push the envelope.

DR. LoCICERO: Good. I want to offer the Panel an opportunity to make any final comments at this point. All of you have an opportunity to speak out. I'll recognize anybody in any order. I think we're talked out.

I would really like to thank the FDA, the sponsors, the open public speakers for participation. Particularly, I would like to thank the FDA for their receptiveness, the really thoughtful questions that they have asked, the response to, you know, our incessant asking for more data. And I would also like to thank Mr. Swink for putting this together and the rest of the staff for making this very smooth.

At this time, the meeting of the General and Plastic Surgical Devices Panel for August 30th and 31st is closed. Thank you.

(Whereupon, at 4:10 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

GENERAL AND PLASTIC SURGERY DEVICES PANEL

August 31, 2011

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

_____

Cathy Belka

Official Reporter

Free State Reporting, Inc.
1378 Cape Saint Claire Road
Annapolis, MD 21409
(410) 974-0947